```
=> d his

     (FILE 'HOME' ENTERED AT 07:24:46 ON 19 DEC 2003)
               SET COST OFF

     FILE 'REGISTRY' ENTERED AT 07:25:05 ON 19 DEC 2003
               E MELPHALAN/CN
L1             1 S E3
               E C13H18CL2N2O2/MF
L2            79 S E3 AND 46.150.18/RID AND 1/NR
L3            67 S L2 NOT PHENYLALANINE
L4            61 S L3 NOT ALANINE
L5            18 S L2 NOT L4
L6             5 S L5 AND 4
L7             3 S L6 NOT (T/ELS OR 14C2)
L8             3 S L1,L7
               SEL RN
L9            24 S E1-E3/CRN
L10           18 S L9 NOT PMS/CI
L11           17 S L10 NOT C5-C6-C6-C6/ES
L12            6 S L9 NOT L10
L13            1 S L12 AND 1/NC

     FILE 'HCAPLUS' ENTERED AT 07:36:13 ON 19 DEC 2003
L14         2851 S L8
L15         2642 S MELPHALAN OR MELFALAN
L16         1027 S SARCOCLORIN# OR SARCOLYSIN# OR SARKOLYSIN# OR MEDPHALAN OR ME
L17          260 S NSC241286 OR NSC8806 OR NSC()(241286 OR 241 286 OR 8806) OR 3
L18          268 S L11
L19            2 S L13
L20            9 S MERPHALAN OR MERFALAN
L21          399 S 3 P BIS 2 CHLOROETHYL AMINO PHENYL (L) ALANINE
L22          786 S SARCOLYSIN#

     FILE 'REGISTRY' ENTERED AT 07:43:01 ON 19 DEC 2003
               E THALIDOMIDE/CN
L23            1 S E3
               SEL RN
L24           57 S E1/CRN
L25            2 S L24 NOT MXS/CI

     FILE 'HCAPLUS' ENTERED AT 07:46:05 ON 19 DEC 2003
L26         1481 S L23 OR L25
L27         1755 S THALIDOMID#
L28           83 S TALINOL OR TALIMOL OR SUARAMIDE OR SOFTENON OR SOFTENIL OR SE
L29            0 S NSC527179 OR NSC66847 OR NSC()(527179 OR 527 179 OR 66847 OR

     FILE 'REGISTRY' ENTERED AT 07:46:57 ON 19 DEC 2003
               E ERYTHROPOIETIN/CN
L30            1 S E3
               SEL RN
L31            6 S E1/CRN
               E ERYTHROPOIETIN
L32         1239 S E3
L33         1233 S L32 AND 1/NC

     FILE 'HCAPLUS' ENTERED AT 07:48:26 ON 19 DEC 2003
L34         7864 S L30
L35         8120 S L33
L36        10336 S ERYTHROPOIETIN OR EPOETIN OR EPOGIS OR HEMPOIETIN# OR HAEMPOI
L37         4034 S L14-L22
L38        12363 S L26-L29,L34-L36
L39        29773 S IL6 OR IL15 OR (IL OR INTERLEUKIN)()(6 OR 15)
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                E INTERLEUKIN/CT
                E E45+ALL
L40         1360 S E8,E7
                E E6+ALL
L41        19943 S E40,E58
L42         2073 S L39-L41 AND ANTAGON?
                E MULTIPLE MYELOMA/CT
                E E3+ALL
L43         6756 S E7-E10,E6
L44        16144 S E6-E13,E15-E16/BI
L45          258 S KAHLER? DISEASE OR KAHLER S DISEASE OR (PLASMA!CELL OR PLASMA
                E E17+ALL
L46        16171 S L43-L45
                E BISPHOSPHON/CT
                E DIPHOSPHON/CT
                E E6+ALL
                E E2+ALL
L47         2833 S E4
L48         6253 S (DIPHOSPHORIC OR BISPHOSPHORIC)()ACID OR DIPHOSPHONATE OR BIS

     FILE 'REGISTRY' ENTERED AT 07:56:17 ON 19 DEC 2003
L49            1 S 13598-36-2

     FILE 'HCAPLUS' ENTERED AT 07:56:33 ON 19 DEC 2003
L50         3228 S L49/D
L51        10651 S L47,L48,L50

     FILE 'REGISTRY' ENTERED AT 07:57:20 ON 19 DEC 2003
L52            1 S 129318-43-0
L53              STR
L54           50 S L53
L55       103129 S L53 FUL
L56        47349 S L55 AND 2/P
L57        46762 S L56 NOT SQL/FA
L58        46596 S L57 NOT MXS/CI
L59        44634 S L58 NOT PMS/CI
L60        37599 S L59 NOT (COMPD OR WITH OR UNSPECIFIED OR IDS/CI)
L61        .9750 S L56 NOT L60

     FILE 'HCAPLUS' ENTERED AT 08:00:18 ON 19 DEC 2003
L62        88509 S L60
L63        42544 S L61
L64       138425 S L38,L42,L51,L62,L63
L65          601 S L64 AND L46
L66         2928 S (ALPHA4 OR ALPHAIV OR 4ALPHA OR IVALPHA OR ALFA4 OR ALFAIV OR
                E INTEGRIN/CT
                E E11+ALL
L67         2296 S E2
L68         1570 S E4
L69            5 S L65 AND L68
L70            5 S L65 AND L67
L71          412 S L14-L22 AND L46
L72            6 S L71 AND L66,L67
L73            8 S L69,L70,L72
L74            9 S L71 AND INTEGRIN
L75           19 S L65 AND INTEGRIN
L76           25 S L73-L75
                E MUNDY G
                E MUNDY G/AU
L77          279 S E3,E6,E8-E10
                E YONEDA T/AU
L78           67 S E3
                E YONEDA TOSH/AU
```

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L79          129 S E4,E16-E19
L80            2 S L76 AND L77-L79
L81            7 S L76 AND (PD<=19990913 OR PRD<=19990913 OR AD<=19990913)
L82            7 S L80,L81
L83           46 S L14-L22,L64 AND L67,L68
L84          580 S L14-L22,L64 AND INTEGRIN
L85          287 S L83,L84 AND (PD<=19990913 OR PRD<=19990913 OR AD<=19990913)
L86           84 S L85 AND (PHARMACOL? OR PHARMACEUT?)/SC,SX
L87           71 S L85 AND IMMUN?/SC,SX
L88          138 S L86,L87
                 E BONE/CT
                 E E3+ALL
L89           18 S L85 AND E9,E8+NT
                 E E33+ALL
L90           23 S L85 AND E7,E8,E6+NT
                 E E118+ALL
L91            7 S L85 AND (E31+NT OR E32+NT OR E34+NT OR E35+NT OR E36+NT OR E3
L92           35 S L89-L91
                 SEL DN AN 1 3 15 20 22 23
L93            6 S L92 AND E1-E18
L94           10 S L82,L93 AND L14-L22,L26-L29,L34-L48,L50,L51,L62-L93
                 SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 08:28:37 ON 19 DEC 2003
L95           11 S E19-E29

     FILE 'HCAPLUS' ENTERED AT 08:28:56 ON 19 DEC 2003
                 SEL RN L80

     FILE 'REGISTRY' ENTERED AT 08:29:00 ON 19 DEC 2003
L96           19 S E30-E48
L97           15 S L96 NOT L95

=> fil reg
FILE 'REGISTRY' ENTERED AT 08:31:48 ON 19 DEC 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   18 DEC 2003  HIGHEST RN 627518-95-0
DICTIONARY FILE UPDATES:  18 DEC 2003  HIGHEST RN 627518-95-0

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d sta que l56
L53             STR
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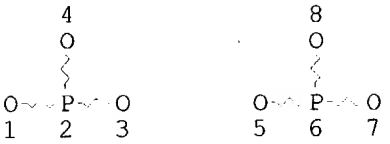


Open structure search for "bis-phosphonate"

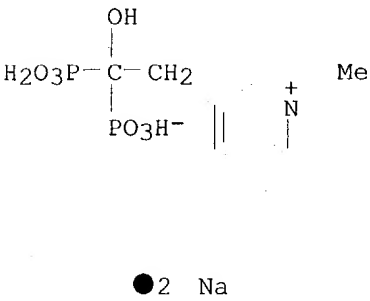
NODE ATTRIBUTES:
CONNECT IS E1 RC AT 4
CONNECT IS E1 RC AT 8
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 8

STEREO ATTRIBUTES: NONE
L55 103129 SEA FILE=REGISTRY SSS FUL L53
L56 47349 SEA FILE=REGISTRY ABB=ON PLU=ON L55 AND 2/P

=> d ide can tot 195

L95 ANSWER 1 OF 11 REGISTRY COPYRIGHT 2003 ACS on STN
RN **197313-76-1** REGISTRY
CN Pyridinium, 3-(2-hydroxy-2,2-diphosphonoethyl)-1-methyl-, inner salt, disodium salt (9CI) (CA INDEX NAME)
OTHER NAMES:
CN NE 10244
MF C8 H13 N O7 P2 . 2 Na
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, TOXCENTER, USPATFULL
CRN (154618-13-0)



Hit compounds for rep 1-10, Set L94

6 REFERENCES IN FILE CA (1907 TO DATE)
6 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:346153

REFERENCE 2: 137:746

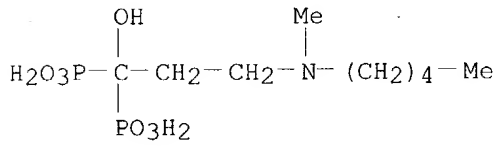
REFERENCE 3: 136:74620

REFERENCE 4: 134:524

REFERENCE 5: 133:129623

REFERENCE 6: 127:302970

L95 ANSWER 2 OF 11 REGISTRY COPYRIGHT 2003 ACS on STN
RN **114084-78-5** REGISTRY
CN Phosphonic acid, [1-hydroxy-3-(methylpentylamino)propylidene]bis- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Ibandronate
CN Ibandronic acid
CN [1-Hydroxy-3-(methylpentylamino)propylidene]diphosphonic acid
FS 3D CONCORD
MF C9 H23 N O7 P2
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CIN, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

233 REFERENCES IN FILE CA (1907 TO DATE)
16 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
234 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:399810

REFERENCE 2: 139:399744

REFERENCE 3: 139:386433

REFERENCE 4: 139:381614

REFERENCE 5: 139:375605

REFERENCE 6: 139:358707

REFERENCE 7: 139:358664

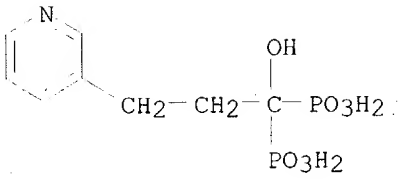
REFERENCE 8: 139:345883

REFERENCE 9: 139:333047

REFERENCE 10: 139:333016

L95 ANSWER 3 OF 11 REGISTRY COPYRIGHT 2003 ACS on STN
RN **104261-69-0** REGISTRY
CN Phosphonic acid, [1-hydroxy-3-(3-pyridinyl)propylidene]bis- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Homorisedronate
CN NE 58051

FS 3D CONCORD
MF C8 H13 N O7 P2
CI COM
SR CA
LC STN Files: BIOSIS, CA, CANCERLIT, CAPLUS, MEDLINE, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

14 REFERENCES IN FILE CA (1907 TO DATE)
14 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 137:163321

REFERENCE 2: 137:134485

REFERENCE 3: 137:27796

REFERENCE 4: 136:63613

REFERENCE 5: 134:289962

REFERENCE 6: 133:129623

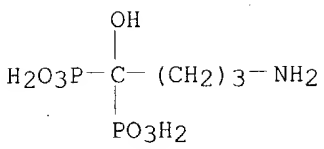
REFERENCE 7: 130:162737

REFERENCE 8: 130:119056

REFERENCE 9: 127:302970

REFERENCE 10: 125:316225

L95 ANSWER 4 OF 11 REGISTRY COPYRIGHT 2003 ACS on STN
RN **66376-36-1** REGISTRY
CN Phosphonic acid, (4-amino-1-hydroxybutylidene)bis- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 4-Amino-1-hydroxybutane-1,1-diphosphonate
CN 4-Amino-1-hydroxybutane-1,1-diphosphonic acid
CN 4-Amino-1-hydroxybutane-1,1-diyldiphosphonic acid
CN 4-Amino-1-hydroxybutylidene-1,1-bis(phosphonic acid)
CN ABDP
CN Alendronate
CN Alendronic acid
FS 3D CONCORD
MF C4 H13 N O7 P2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

814 REFERENCES IN FILE CA (1907 TO DATE)
35 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
815 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:399810

REFERENCE 2: 139:399744

REFERENCE 3: 139:391129

REFERENCE 4: 139:386594

REFERENCE 5: 139:377743

REFERENCE 6: 139:375605

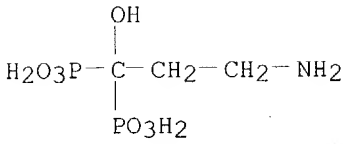
REFERENCE 7: 139:374478

REFERENCE 8: 139:374114

REFERENCE 9: 139:369534

REFERENCE 10: 139:358460

L95 ANSWER 5 OF 11 REGISTRY COPYRIGHT 2003 ACS on STN
RN **40391-99-9** REGISTRY
CN Phosphonic acid, (3-amino-1-hydroxypropylidene)bis- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (α-Hydroxy-γ-aminopropylidene)diphosphonic acid
CN (3-Amino-1-hydroxypropylidene)-1,1-bisphosphonate
CN 3-Amino-1-hydroxypropane-1,1-diphosphonic acid
CN 3-Amino-1-hydroxypropylidene-1,1-bisphosphonic acid
CN 3-Amino-1-hydroxypropylidenediphosphonic acid
CN ADP
CN AHPrBP
CN Amidronic acid
CN Pamidronic acid
CN Propane-1-hydroxy-3-amino-1,1-diphosphonic acid
FS 3D CONCORD
MF C3 H11 N O7 P2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

710 REFERENCES IN FILE CA (1907 TO DATE)
35 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
713 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:399810

REFERENCE 2: 139:399744

REFERENCE 3: 139:375605

REFERENCE 4: 139:374196

REFERENCE 5: 139:345882

REFERENCE 6: 139:345853

REFERENCE 7: 139:345845

REFERENCE 8: 139:345414

REFERENCE 9: 139:333017

REFERENCE 10: 139:333015

L95 ANSWER 6 OF 11 REGISTRY COPYRIGHT 2003 ACS on STN
RN **13598-36-2** REGISTRY
CN Phosphonic acid (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN Dihydroxyphosphine oxide
CN Phosphorous acid
MF H3 O3 P
CI COM
LC STN Files: AGRICOLA, ANABSTR, AQUIRE, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DETHERM*, DIPPR*, EMBASE, IFICDB, IFIPAT, IFIUDB, MRCK*, MSDS-OHS, NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, TOXCENTER, TULSA, USPAT2, USPATFULL, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
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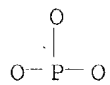


*** FRAGMENT DIAGRAM IS INCOMPLETE ***
6526 REFERENCES IN FILE CA (1907 TO DATE)
3216 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
6541 REFERENCES IN FILE CAPLUS (1907 TO DATE)

8 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 139:399744

REFERENCE 2: 139:398459

REFERENCE 3: 139:397764

REFERENCE 4: 139:397762

REFERENCE 5: 139:397760

REFERENCE 6: 139:397734

REFERENCE 7: 139:392516

REFERENCE 8: 139:392514

REFERENCE 9: 139:390929

REFERENCE 10: 139:390578

L95 ANSWER 7 OF 11 REGISTRY COPYRIGHT 2003 ACS on STN
RN **11096-26-7** REGISTRY
CN Erythropoietin (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Ep
CN EPO
CN Epoetin
CN Epogis S
CN Hempoietine
MF Unspecified
CI COM, MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
7848 REFERENCES IN FILE CA (1907 TO DATE)
194 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
7864 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:399815

REFERENCE 2: 139:392436

REFERENCE 3: 139:391734

REFERENCE 4: 139:391733

REFERENCE 5: 139:391446

REFERENCE 6: 139:391445

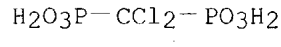
REFERENCE 7: 139:391354

REFERENCE 8: 139:386430

REFERENCE 9: 139:386408

REFERENCE 10: 139:379540

L95 ANSWER 8 OF 11 REGISTRY COPYRIGHT 2003 ACS on STN
RN **10596-23-3** REGISTRY
CN Phosphonic acid, (dichloromethylene)bis- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phosphonic acid, (dichloromethylene)di- (8CI)
OTHER NAMES:
CN (Dichloromethylene)bis[phosphonic acid]
CN Cl 2MDP
CN Clodronic acid
CN Dichloromethylenediphosphonic acid
CN DMDP
CN Methanedichlorodiphosphonic acid
FS 3D CONCORD
DR 163706-60-3
MF C H4 Cl2 O6 P2
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CHEMLIST, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

706 REFERENCES IN FILE CA (1907 TO DATE)
33 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
706 REFERENCES IN FILE CAPLUS (1907 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 139:399810

REFERENCE 2: 139:399744

REFERENCE 3: 139:375605

REFERENCE 4: 139:358679

REFERENCE 5: 139:345878

REFERENCE 6: 139:345877

REFERENCE 7: 139:345738

REFERENCE 8: 139:345414

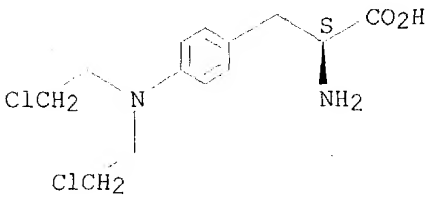
REFERENCE 9: 139:345263

REFERENCE 10: 139:332639

L95 ANSWER 9 OF 11 REGISTRY COPYRIGHT 2003 ACS on STN
RN **148-82-3** REGISTRY

CN L-Phenylalanine, 4-[bis(2-chloroethyl)amino]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Alanine, 3-[p-[bis(2-chloroethyl)amino]phenyl]-, L- (8CI)
OTHER NAMES:
CN 3025CB
CN Alanine nitrogen mustard
CN Alkeran
CN CB 3025
CN L-PAM
CN L-Phenylalanine mustard
CN L-Phenylalanine mustard hydrochloride
CN L-Sarcolysin
CN L-Sarcolysine
CN L-Sarkolysin
CN Levofalan
CN Levofolan
CN Levopholan
CN Melfalan
CN Melphalan
CN NSC 241286
CN NSC 8806
CN Phenylalanine mustard
CN Sarcoclorin
FS STEREOSEARCH
DR 8057-25-8
MF C13 H18 Cl2 N2 O2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PHAR, PROMT, RTECS*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2656 REFERENCES IN FILE CA (1907 TO DATE)
150 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2662 REFERENCES IN FILE CAPLUS (1907 TO DATE)
21 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 139:399770

REFERENCE 2: 139:395950

REFERENCE 3: 139:395828

REFERENCE 4: 139:395827

REFERENCE 5: 139:391354

REFERENCE 6: 139:391341

REFERENCE 7: 139:390794

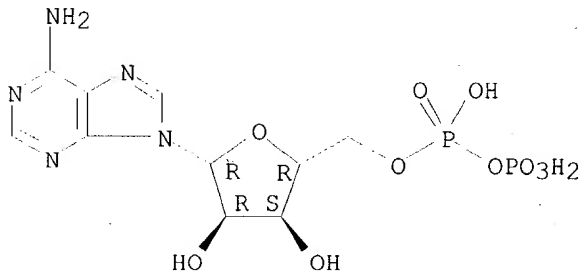
REFERENCE 8: 139:390793

REFERENCE 9: 139:380023

REFERENCE 10: 139:374995

L95 ANSWER 10 OF 11 REGISTRY COPYRIGHT 2003 ACS on STN
RN **58-64-0** REGISTRY
CN Adenosine 5'-(trihydrogen diphosphate) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Adenosine 5'-(trihydrogen pyrophosphate) (8CI)
CN Adenosine diphosphate (6CI)
OTHER NAMES:
CN α-ADP
CN 5'-ADP
CN Adenosine 5'-diphosphate
CN Adenosine 5'-diphosphoric acid
CN Adenosine 5'-pyrophosphate
CN Adenosine 5'-pyrophosphoric acid
CN Adenosine pyrophosphate
CN Adenosine, 5'-(trihydrogen diphosphate)
CN ADP
CN ADP (nucleotide)
FS STEREOSEARCH
DR 84412-16-8
MF C10 H15 N5 O10 P2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NIOSHTIC, PIRA, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

23590 REFERENCES IN FILE CA (1907 TO DATE)
521 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
23601 REFERENCES IN FILE CAPLUS (1907 TO DATE)
22 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 139:394373

REFERENCE 2: 139:393749

REFERENCE 3: 139:392855

REFERENCE 4: 139:392819

REFERENCE 5: 139:392740

REFERENCE 6: 139:391641

REFERENCE 7: 139:391620

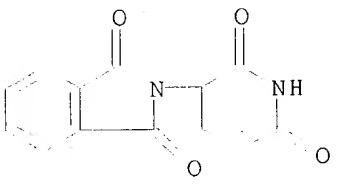
REFERENCE 8: 139:391619

REFERENCE 9: 139:391604

REFERENCE 10: 139:379964

L95 ANSWER 11 OF 11 REGISTRY COPYRIGHT 2003 ACS on STN
RN **50-35-1** REGISTRY
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phthalimide, N-(2,6-dioxo-3-piperidyl)- (6CI, 7CI, 8CI)
OTHER NAMES:
CN (±)-Thalidomide
CN α-(N-Phthalimido)glutarimide
CN α-N-Phthalylglutaramide
CN α-Phthalimidoglutarimide
CN 1,3-Dioxo-2-(2,6-dioxopiperidin-3-yl)isoindoline
CN 3-Phthalimidoglutarimide
CN Celgene
CN Contergan
CN Distaval
CN K 17
CN Kevadon
CN Myrin
CN N-(2,6-Dioxo-3-piperidyl)phthalimide
CN N-Phthaloylglutamimide
CN Neurosedyn
CN NSC 527179
CN NSC 66847
CN Pantosediv
CN Quetimid
CN Sedalis
CN Sedoval
CN Softenil
CN Softenon
CN Suaramide
CN Talimol
CN Talinol
CN Thalidomide
CN Thalomid
FS 3D CONCORD
DR 14088-68-7, 731-40-8
MF C13 H10 N2 O4
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU,

DIOGENES, DRUGU, EMBASE, HODOC*, HSDB*, IMSCOSEARCH, IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PHAR, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1474 REFERENCES IN FILE CA (1907 TO DATE)
83 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1480 REFERENCES IN FILE CAPLUS (1907 TO DATE)
15 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 139:395772

REFERENCE 2: 139:390791

REFERENCE 3: 139:390702

REFERENCE 4: 139:390487

REFERENCE 5: 139:390456

REFERENCE 6: 139:375014

REFERENCE 7: 139:374504

REFERENCE 8: 139:374401

REFERENCE 9: 139:374323

REFERENCE 10: 139:373879

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 08:32:18 ON 19 DEC 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 19 Dec 2003 VOL 139 ISS 26

FILE LAST UPDATED: 18 Dec 2003 (20031218/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L94 ANSWER 1 OF 10 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **2002:833305** HCAPLUS
DN **137:333131**
ED Entered STN: 01 Nov 2002
TI Methods of treating **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists**
IN **Mundy, Gregory R.; Yoneda, Toshiyuki**
PA Board of Regents, The University of Texas System, USA
SO U.S. Pat. Appl. Publ., 64 pp., Cont.-in-part of U.S. Ser. No. 943,659.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K039-395
NCL 424143100
CC 1-6 (**Pharmacology**)
Section cross-reference(s): **15**

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002159998	A1	20021031	US 2002-86217	20020221 <--
	WO 2000015247	A2	20000323	WO 1999-US21170	19990913 <--
	WO 2000015247	A3	20000525		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2002022028	A1	20020221	US 2001-805840	20010313 <--
	US 2002041874	A1	20020411	US 2001-943659	20010831 <--
PRAI	US 1998-100182P	P	19980914 <--		
	WO 1999-US21170	A1	19990913 <--		
	US 2001-805840	A2	20010313		
	US 2001-943659	A2	20010831		

AB **Antagonists** of **.alpha.4 integrin/.** **alpha.4 integrin** ligand adhesion, which inhibit the biol. effects of such adhesion are described and methods for their use are detailed. Such **antagonists** are useful in suppressing bone destruction associated with **multiple myeloma**. The homing of **multiple myeloma** cells to bone marrow and their **.alpha.4 integrin** -dependent release of bone-resorbing factors, resulting in bone destruction in patients with **multiple myeloma**, is inhibited.

ST **integrin antagonist** antibody chemotherapeutic agent **myeloma** treatment

IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(LPAM-1 (lymphocyte Peyer's patch high endothelial venule adhesion mol. 1); treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT Cell adhesion molecules
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(VCAM-1, antibodies to; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT **Interleukin 15**
Interleukin 6
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**antagonists**; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT Antibodies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chimeric; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT Antibodies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(humanized; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT Antitumor agents
(**multiple myeloma**; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT **Bone marrow, disease**
(neoplasm; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT **Bone**
(resorption, inhibitors; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT Human
Multiple myeloma
Osteoclast
(treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α **4**, antibodies to; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α **4**β **1**; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT 410084-86-5P, BIO 8809
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(BIO 8809; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT **13598-36-2D**, Phosphonic acid, alkylidinebis- derivs.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate**; treatment of **multiple**

myeloma and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT **148-82-3, Melphalan**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT 98-09-9, Benzenesulfonyl chloride 6404-29-1 148893-10-1 174569-25-6 409325-33-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

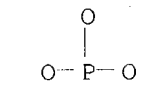
IT 327613-69-4P 409325-34-4P 409325-35-5P 409325-36-6P 409325-37-7P 409325-38-8P 473806-21-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT 410084-88-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT **50-35-1, Thalidomide 11096-26-7, Erythropoietin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT **13598-36-2D**, Phosphonic acid, alkylidinebis- derivs.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate**; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

RN 13598-36-2 HCAPLUS
CN Phosphonic acid (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)

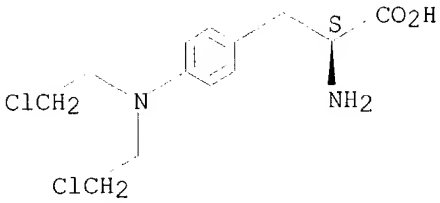


*** FRAGMENT DIAGRAM IS INCOMPLETE ***

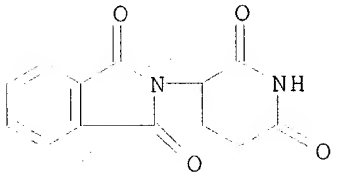
IT **148-82-3, Melphalan**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

RN 148-82-3 HCAPLUS
CN L-Phenylalanine, 4-[bis(2-chloroethyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **50-35-1, Thalidomide 11096-26-7, Erythropoietin**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)
RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

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L94 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **2002:276427** HCAPLUS
DN **136:304051**
ED Entered STN: 12 Apr 2002
TI Methods of treating **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists**
IN **Mundy, Gregory R.; Yoneda, Toshiyuki**
PA Board of Regents, University of Texas System, USA
SO U.S. Pat. Appl. Publ., 61 pp., Cont.-in-part of U.S. Ser. No. 805,840.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K039-395
NCL 424131100
CC 1-6 (**Pharmacology**)
Section cross-reference(s): **15**
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2002041874	A1	20020411	US 2001-943659	20010831 <--
WO 2000015247	A2	20000323	WO 1999-US21170	19990913 <--
WO 2000015247	A3	20000525		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,

ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

	US 2002022028	A1	20020221	US 2001-805840	20010313	<--
	US 2002159998	A1	20021031	US 2002-86217	20020221	<--
PRAI	US 1998-100182P	P	19980914	<--		
	WO 1999-US21170	W	19990913	<--		
	US 2001-805840	A2	20010313			
	US 2001-943659	A2	20010831			

AB **Antagonists** of **.alpha.4 integrin/.** **alpha.4 integrin** ligand adhesion, which inhibit the biol. effects of such adhesion are described and methods for their use are detailed. Such **antagonists** are useful in suppressing bone destruction associated with **multiple myeloma.** The homing of **multiple myeloma** cells to bone marrow and their **.alpha.4 integrin** -dependent release of bone-resorbing factors, resulting in bone destruction in patients with **multiple myeloma,** is inhibited. Among the examples provided are 2 which show that monoclonal antibody PS/2 to VLA-4 strongly inhibits the growth of established **myeloma** cells and that anti-**.alpha.4 integrin** antibody enhances sensitivity of **myeloma** cells to **melphalan.**

ST **integrin antagonist** antibody chemotherapeutic agent **myeloma** treatment

IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(LPAM-1 (lymphocyte Peyer's patch high endothelial venule adhesion mol. 1); treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT Cell adhesion molecules
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(VCAM-1, antibodies to; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT **Interleukin 15**
Interleukin 6
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**antagonists;** treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT Antibodies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chimeric; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT Antibodies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(humanized; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT Antibodies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(monoclonal; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT Antitumor agents
(**multiple myeloma;** treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT **Bone marrow, disease**
(neoplasm; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT **Bone**
(resorption, inhibitors; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT Antitumor agents
Drug interactions
Human
Osteoclast
(treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α **4**, antibodies to; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α **4**β **1**; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT 410084-86-5P, BIO 8809
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(BIO 8809; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT 410084-88-7P, BIO 9257
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(BIO 9257; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

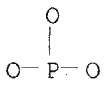
IT **13598-36-2D**, Phosphonic acid, alkylidenebis- derivs.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate**; treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT **148-82-3, Melphalan**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT 98-09-9, Benzenesulfonyl chloride 174569-25-6 409325-33-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

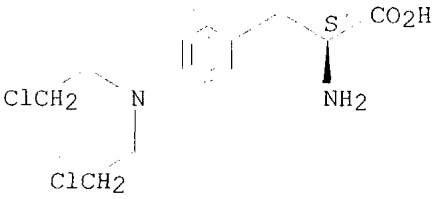
IT 189215-90-5P 327613-69-4P 409325-34-4P 409325-35-5P 409325-36-6P 409325-37-7P 409325-38-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(treatment of **multiple myeloma** and **myeloma**-induced bone resorption using **integrin antagonists** and chemotherapeutic agents)

IT **50-35-1, Thalidomide 11096-26-7,**
Erythropoietin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of **multiple myeloma** and **myeloma**
-induced bone resorption using **integrin antagonists**
and chemotherapeutic agents)
IT **13598-36-2D**, Phosphonic acid, alkylidenebis- derivs.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate**; treatment of **multiple**
myeloma and **myeloma**-induced bone resorption using
integrin antagonists and chemotherapeutic agents)
RN 13598-36-2 HCAPLUS
CN Phosphonic acid (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)

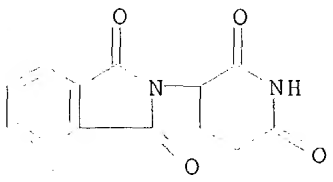


*** FRAGMENT DIAGRAM IS INCOMPLETE ***
IT **148-82-3, Melphalan**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(treatment of **multiple myeloma** and **myeloma**
-induced bone resorption using **integrin antagonists**
and chemotherapeutic agents)
RN 148-82-3 HCAPLUS
CN L-Phenylalanine, 4-[bis(2-chloroethyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **50-35-1, Thalidomide 11096-26-7,**
Erythropoietin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of **multiple myeloma** and **myeloma**
-induced bone resorption using **integrin antagonists**
and chemotherapeutic agents)
RN 50-35-1 HCAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



RN 11096-26-7 HCAPLUS
CN Erythropoietin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L94 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:351801 HCAPLUS
DN 131:16005
ED Entered STN: 08 Jun 1999
TI Establishment and characterization of a CD95 (Fas/Apo-1)-negative **myeloma** cell line
AU Kuribayashi, Noriomi; Hata, Hiroyuki; Yoshida, Minoru; Sonoku, Takashi; Nagasaki, Akitoshi; Kimura, Tatsuya; Harada, Naoko; Matsuzaki, Hiromitsu
CS Second Dep. Internal Medicine, School Medicine, Kumamoto Univ., Kumamoto, 860, Japan
SO Acta Haematologica (**1999**), 101(3), 113-118
CODEN: ACHAAH; ISSN: 0001-5792
PB S. Karger AG
DT Journal
LA English
CC 9-11 (Biochemical Methods)
Section cross-reference(s): **15**
AB Although expression of CD95 (Fas/Apo-1) on **myeloma** cells was reported, its significance is not clearly understood. The authors established a **myeloma** cell line, KHM-11ad (11ad), from a parental cell line, KHM-11, by collecting cells adhered to a plastic dish. KHM-11 cells were pos. for CD45 and CD95 (Fas/ Apol), and neg. for a myelomonocytic antigen, CD13. CD95 was not detected in 11ad. Expression of CD45 was also decreased in 11ad cells while expression of CD13 was detected in these cells. The growth rate of 11ad cells was 1.7 times lower than that of KHM-11 cells. Anal. of adhesion mols. showed that expression of VLA4 and CD44 was significantly suppressed in 11ad. The IC50 of **melphalan** (**L-PAM**) for 11ad cells was 50 times higher than that for KHM-11, indicating that 11ad is significantly refractory to **L-PAM** than KHM-11 cells. Induction of apoptosis by doxorubicin and cycloheximide was suppressed in 11ad cells compared with those in KHM-11 cells. Western blot for Bcl-2 family of proteins showed that Bax was expressed at a 2.2 times lower level in 11ad cells than in KHM-11 cells while there was no difference in expression of Bcl-2, Bcl-Xs nor Bcl-Xy. These results suggest that CD95-neg. **myeloma** cells may have characteristics as follows: (1) slow proliferation; (2) low sensitivity to apoptosis; (3) low expression of VLA4, CD44 and Bax. Although these intraclonal variations were based on the findings of cell lines, these may reflect similar variations in vivo. The 11ad line may be a suitable model for analyzing intraclonal variation of **myeloma** cells.
ST **myeloma** cell line KHM11ad antigen apoptosis
IT Proteins, specific or class
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(Bax; doxorubicin and cycloheximide effect on KHM-11ad as CD95 (Fas/Apo-1)-neg. **myeloma** cell line)
IT Proteins, specific or class
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(Bcl-x, XL; doxorubicin and cycloheximide effect on KHM-11ad as CD95 (Fas/Apo-1)-neg. **myeloma** cell line)
IT Proteins, specific or class
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(Bcl-x, Xs; doxorubicin and cycloheximide effect on KHM-11ad as CD95 (Fas/Apo-1)-neg. **myeloma** cell line)
IT **Multiple myeloma**
(CD95 (Fas/Apo-1)-neg. **myeloma** cell line establishment and characterization)
IT CD19 (antigen)

CD2 (antigen)
CD20 (antigen)
CD3 (antigen)
CD38 (antigen)
CD4 (antigen)
CD44 (antigen)
CD45 (antigen)
CD5 (antigen)
CD7 (antigen)
Fas antigen
LFA-1 (antigen)
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(CD95 (Fas/Apo-1)-neg. **myeloma** cell line establishment and characterization)

IT Glycoproteins, specific or class
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(H-CAM (homing cell adhesion mol.); CD95 (Fas/Apo-1)-neg. **myeloma** cell line establishment and characterization)

IT Histocompatibility antigens
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(HLA-DR; CD95 (Fas/Apo-1)-neg. **myeloma** cell line establishment and characterization)

IT Cell adhesion molecules
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(ICAM-1 (intercellular adhesion mol. 1); CD95 (Fas/Apo-1)-neg. **myeloma** cell line establishment and characterization)

IT Animal cell line
(KHM-11; CD95 (Fas/Apo-1)-neg. **myeloma** cell line establishment and characterization)

IT Proteins, specific or class
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(bcl-2; doxorubicin and cycloheximide effect on KHM-11ad as CD95 (Fas/Apo-1)-neg. **myeloma** cell line)

IT Apoptosis
(doxorubicin and cycloheximide effect on KHM-11ad as CD95 (Fas/Apo-1)-neg. **myeloma** cell line)

IT **Integrins**
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(α **4β 1**; CD95 (Fas/Apo-1)-neg. **myeloma** cell line establishment and characterization)

IT **Integrins**
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(α5β1; CD95 (Fas/Apo-1)-neg. **myeloma** cell line establishment and characterization)

IT 9054-63-1 82707-54-8, CD10 antigen
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)

(CD95 (Fas/Apo-1)-neg. **myeloma** cell line establishment and characterization)

IT 66-81-9, Cycloheximide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cycloheximide effect on apoptosis of KHM-11ad as CD95 (Fas/Apo-1)-neg. **myeloma** cell line)

IT 23214-92-8, Doxorubicin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(doxorubicin effect on apoptosis of KHM-11ad as CD95 (Fas/Apo-1)-neg. **myeloma** cell line)

IT **148-82-3, Melphalan**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**melphalan** effect on apoptosis of KHM-11ad as CD95 (Fas/Apo-1)-neg. **myeloma** cell line)

RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD

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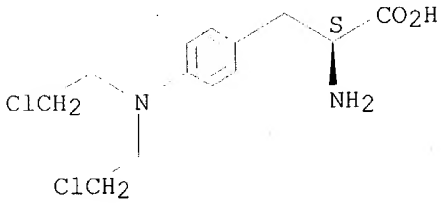
IT **148-82-3, Melphalan**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**melphalan** effect on apoptosis of KHM-11ad as CD95 (Fas/Apo-1)-neg. **myeloma** cell line)

RN 148-82-3 HCAPLUS
CN L-Phenylalanine, 4-[bis(2-chloroethyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L94 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:153899 HCAPLUS
DN 131:321
ED Entered STN: 10 Mar 1999
TI Cell adhesion-mediated drug resistance (CAM-DR): role of **integrins** and resistance to apoptosis in human **myeloma** cell lines
AU Damiano, Jason S.; Cress, Anne E.; Hazlehurst, Lori A.; Shtil, Alexander A.; Dalton, William S.

CS H. Lee. Moffitt Cancer Center, University of South Florida, Tampa, FL, 33612, USA
SO Blood (**1999**), 93(5), 1658-1667
CODEN: BLOOAW; ISSN: 0006-4971
PB W. B. Saunders Co.
DT Journal
LA English
CC 1-6 (**Pharmacology**)
AB **Integrin**-mediated adhesion influences cell survival and may prevent programmed cell death. Little is known about how drug-sensitive tumor cell lines survive initial exposures to cytotoxic drugs and eventually select for drug-resistant populations. Factors that allow for cell survival following acute cytotoxic drug exposure may differ from drug resistance mechanisms selected for by chronic drug exposure. The authors show here that drug-sensitive 8226 human **myeloma** cells, demonstrated to express both VLA-**4** (**.alpha.4** β1) and VLA-5 (α5β1) **integrin** fibronectin (FN) receptors, are relatively resistant to the apoptotic effects of doxorubicin and **melphalan** when pre-adhered to FN and compared with cells grown in suspension. This cell adhesion-mediated drug resistance, or CAM-DR, was not due to reduced drug accumulation or upregulation of anti-apoptotic Bcl-2 family members. As determined by flow cytometry, **myeloma** cell lines selected for drug resistance, with either doxorubicin or **melphalan**, overexpress VLA-4. Functional assays revealed a significant increase in **.alpha.4** -mediated cell adhesion in both drug-resistant variants compared with the drug-sensitive parent line. When removed from selection pressure, drug-resistant cell lines reverted to a drug-sensitive and **.alpha** **.4**-low phenotype. Whether VLA-4-mediated FN adhesion offers a survival advantage over VLA-5-mediated adhesion remains to be determined Thus, the authors demonstrated that FN-mediated adhesion confers a survival advantage for **myeloma** cells acutely exposed to cytotoxic drugs by inhibiting drug-induced apoptosis. This finding may explain how some cells survive initial drug exposure and eventually express classical mechanisms of drug resistance such as MDR1 overexpression.
ST cell adhesion drug resistance **integrin**; apoptosis resistance human **myeloma** cell line
IT Animal cell line
(8226; cell adhesion-mediated drug resistance in relation to role of **integrins** and resistance to apoptosis in human **myeloma** cell lines)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(bcl-2; cell adhesion-mediated drug resistance in relation to role of **integrins** and resistance to apoptosis in human **myeloma** cell lines)
IT Apoptosis
Cell adhesion
Cell death
Cytotoxicity
Drug resistance
(cell adhesion-mediated drug resistance in relation to role of **integrins** and resistance to apoptosis in human **myeloma** cell lines)
IT **Integrins**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cell adhesion-mediated drug resistance in relation to role of **integrins** and resistance to apoptosis in human **myeloma** cell lines)
IT Fibronectin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(cell adhesion-mediated drug resistance in relation to role of **integrins** and resistance to apoptosis in human **myeloma** cell lines)

IT **148-82-3, Melphalan**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(cell adhesion-mediated drug resistance in relation to role of **integrins** and resistance to apoptosis in human **myeloma** cell lines)

IT 23214-92-8, Doxorubicin
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cell adhesion-mediated drug resistance in relation to role of **integrins** and resistance to apoptosis in human **myeloma** cell lines)

RE.CNT 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD

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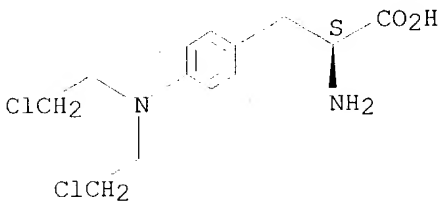
IT **148-82-3, Melphalan**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(cell adhesion-mediated drug resistance in relation to role of **integrins** and resistance to apoptosis in human **myeloma** cell lines)

RN 148-82-3 HCAPLUS
CN L-Phenylalanine, 4-[bis(2-chloroethyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L94 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1998:591855** HCAPLUS
DN **129:211534**
ED Entered STN: 18 Sep 1998
TI Alendronate reduces adhesion of human osteoclast-like cells to bone and bone protein-coated surfaces
AU Colucci, S.; Minielli, V.; Zambonin, G.; Cirulli, N.; Mori, G.; Serra, M.; Patella, V.; Zallone, A. Zambonin; Grano, M.
CS Istituto di Anatomia Umana Normale P.zza G. Cesare, Bari, 70124, Italy
SO Calcified Tissue International (**1998**), 63(3), 230-235
CODEN: CTINDZ; ISSN: 0171-967X
PB Springer-Verlag New York Inc.
DT Journal
LA English
CC 1-10 (**Pharmacology**)
AB **Bisphosphonates** (BPs) are potent inhibitors of bone resorption and are therapeutically effective in disease of increased bone turnover, but their mechanism(s) of action remain to be elucidated. Using as exptl. model human osteoclast-like cell lines derived from giant cell tumors of bone, extensively characterized for their osteoclast features, the adhesive properties were investigated of osteoclasts on bone slices and on

different proteins of the extracellular matrix in the presence of BPs. Adhesion assays using bone slices pretreated with alendronate (ALN), at the established active concentration, showed that, although the morphol. of osteoclasts plated onto pretreated bone slices was not modified, the number of adherent cells was reduced by the treatment of 50% vs. controls. The effect of ALN on the adhesion of osteoclast-like cells onto specific extracellular matrix proteins, such as bone sialoprotein-derived peptide, containing the RGD sequence, conjugated to BSA (BSP-BSA) and fibronectin (FN), was also tested. In the case of FN the treatment with ALN of protein-coated wells did not modify the percentage of cell adhesion compared with the control, whereas onto BSP-BSA the presence of ALN reduced adhesion of about 40-45%, suggesting that the inhibitory effect of ALN on cell adhesion could probably be due to the interference with receptors specifically recognizing bone matrix proteins as $\alpha v\beta 3$ **integrins.** Furthermore, ALN induced Ca-mediated intracellular signals in osteoclasts, triggering a 2-fold increase in intracellular Ca concentration

ST alendronate bone protein adhesion osteoclast antiresorptive

IT Sialoglycoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(BSP II (bone sialoglycoprotein II); cell adhesion on osteoclasts coated with BSP in the presence of alendronate)

IT Cell adhesion
Osteoclast
(alendronate reduces osteoclast adhesion to bone surfaces)

IT Fibronectins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cell adhesion on osteoclasts coated with fibronectin in the presence of alendronate)

IT **Bone**
(resorption, inhibitors; alendronate reduces osteoclast adhesion to bone surfaces)

IT **Osteoporosis**
(therapeutic agents; alendronate reduces osteoclast adhesion to bone surfaces)

IT **66376-36-1**, Alendronate
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(alendronate reduces osteoclast adhesion to bone surfaces)

IT 7440-70-2, Calcium, biological studies
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(effect of alendronate on intracellular Ca concentration in osteoclasts)

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD

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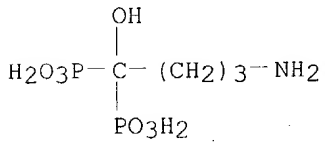
IT **66376-36-1**, Alendronate
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(alendronate reduces osteoclast adhesion to bone surfaces)

RN 66376-36-1 HCAPLUS
CN Phosphonic acid, (4-amino-1-hydroxybutylidene)bis- (9CI) (CA INDEX NAME)



L94 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1997:701081** HCAPLUS
DN **128:30109**
ED Entered STN: 07 Nov 1997
TI Deficient drug transporter function of bone marrow-localized and leukemic plasma cells in **multiple myeloma**
AU Pilarski, Linda M.; Szczepek, Agnieszka J.; Belch, Andrew R.
CS Department of Oncology, University of Alberta and Cross Cancer Institute, Edmonton, AB, Can.
SO Blood (**1997**), 90(9), 3751-3759
CODEN: BLOOAW; ISSN: 0006-4971
PB Saunders
DT Journal
LA English
CC 1-6 (**Pharmacology**)
Section cross-reference(s): 14
AB Although chemotherapy effectively reduces the plasma cell burden in **multiple myeloma** (MM), the disease recurs. MM includes circulating and bone marrow (BM) localized components. A large majority of circulating CD11b+ MM B cells (81%) express an IgH VDJ rearrangement identical to that of autologous BM plasma cells. Unlike plasma cells, these monoclonal circulating B cells exhibit dye and drug transport activity before and throughout chemotherapy. Drug resistance was measured as the ability to export the fluorescent dye Rhodamine 123 (Rh123) or the drug adriamycin, using flow cytometry. The role of P-glycoprotein 170 (P-gp), the multidrug transporter, was defined by cyclosporin A (CsA)-sensitive dye export. Only 8% to 11% of BM-localized plasma cells exported dye with the majority retaining dye, identified as bright staining. Circulating leukemic plasma cells were also unable to export dye and remained Rh123bright. However, 53% of circulating clonotypic MM B cells exhibited CsA-sensitive dye export. BM plasma cells taken before or after initiation of first line chemotherapy were equally unable to export dye. Thus in **myeloma**, differentiation to the plasma cell stage is accompanied by a loss of P-gp function, although P-gp phenotypic

expression is retained. In contrast, for monoclonal gammopathy of undetd. significance (MGUS), 54% of BM-localized plasma cells exported dye, comparable to the 53% of circulating MGUS B cells that also exported dye, suggesting that the apparent defect in P-gp function is unique to **myeloma** plasma cells. Virtually all BM plasma cells in MM retained the drug adriamycin, consistent with their initial drug sensitivity in vivo, in contrast to circulating MM B cells, or to T cells in BM or blood. Thus, circulating B cells appear to be the predominant drug-resistant component of the MM B-lineage hierarchy. This report suggests that successful therapeutic strategies will be those that target circulating B cells. Chemosensitization methods involving inhibition of P-gp are likely to improve depletion of these cells by compromising their ability to exclude drug. This work suggests that circulating clonotypic B cells should be monitored in clin. trials to confirm their depletion and the overall efficacy of novel treatment strategies.

ST **multiple myeloma** drug transport plasma cell; resistance drug B cell **multiple myeloma**

IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antigens CD11b; deficient drug transporter function of bone marrow-localized and leukemic plasma cells in **multiple myeloma**)

IT B cell (lymphocyte)
Bone marrow
CD4-positive T cell
CD8-positive T cell
Drug resistance
Monocyte
Multiple myeloma
(deficient drug transporter function of bone marrow-localized and leukemic plasma cells in **multiple myeloma**)

IT Interferons
Interleukin 2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(deficient drug transporter function of bone marrow-localized and leukemic plasma cells in **multiple myeloma**)

IT P-glycoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(deficient drug transporter function of bone marrow-localized and leukemic plasma cells in **multiple myeloma**)

IT CD14 (antigen)
CD19 (antigen)
CD38 (antigen)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(deficient drug transporter function of bone marrow-localized and leukemic plasma cells in **multiple myeloma**)

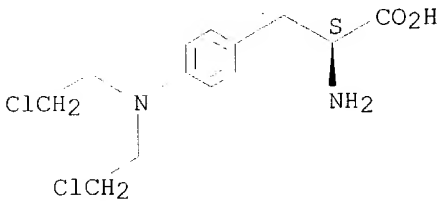
IT Biological transport
(drug; deficient drug transporter function of bone marrow-localized and leukemic plasma cells in **multiple myeloma**)

IT Immunoglobulins
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(monoclonal gammopathy; deficient drug transporter function of bone marrow-localized and leukemic plasma cells in **multiple myeloma**)

IT Antitumor agents
Antitumor agents
Antitumor agents
(**multiple myeloma**; deficient drug transporter function of bone marrow-localized and leukemic plasma cells in **multiple myeloma**)

IT **Leukemia**
(plasma cell, terminal; deficient drug transporter function of bone marrow-localized and leukemic plasma cells in **multiple myeloma**)
IT Lymphocyte
(plasma cell; deficient drug transporter function of bone marrow-localized and leukemic plasma cells in **multiple myeloma**)
IT 25316-40-9, Adriamycin
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(deficient drug transporter function of bone marrow-localized and leukemic plasma cells in **multiple myeloma**)
IT 50-02-2, Dexamethasone 53-03-2, Prednisone 57-22-7, Vincristine **148-82-3, Melphalan**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(deficient drug transporter function of bone marrow-localized and leukemic plasma cells in **multiple myeloma**)
IT **148-82-3, Melphalan**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(deficient drug transporter function of bone marrow-localized and leukemic plasma cells in **multiple myeloma**)
RN 148-82-3 HCAPLUS
CN L-Phenylalanine, 4-[bis(2-chloroethyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L94 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1997:613207** HCAPLUS
DN **127:302970**
ED Entered STN: 26 Sep 1997
TI **Bisphosphonates** inhibit prostate and breast carcinoma cell adhesion to unmineralized and mineralized bone extracellular matrixes
AU Boissier, Sandrine; Magnetto, Sandrine; Frappart, Lucien; Cuzin, Beatrice; Ebetino, Frank H.; Delmas, Pierre D.; Clezardin, Philippe
CS Institut National de la Sante et de la Recherche Medicale Research Unit 403, Pavillon F, Hopital Edouard Herriot, Lyon, 69437, Fr.
SO Cancer Research (**1997**), 57(18), 3890-3894
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
CC 1-6 (**Pharmacology**)
AB The mol. mechanisms by which tumor cells induce osteolytic metastases are likely to involve tumor cell adhesion to bone as well as the release of soluble mediators from tumor cells that stimulate osteoclast-mediated bone resorption. **Bisphosphonates** (BPs) are powerful inhibitors of the osteoclast activity and are, therefore, used in the treatment of

cancer-associated osteolytic metastases. Here, we investigated the effect of BPs on breast and prostate carcinoma cell adhesion to unmineralized and mineralized bone extracellular matrixes. BP pretreatment of tumor cells inhibited tumor cell adhesion to unmineralized and mineralized osteoblastic extracellular matrixes in a dose-dependent manner. In contrast, BP did not affect adhesion of normal cells (fibroblasts) to extracellular matrixes. The order of potency for four BPs in inhibiting tumor cell adhesion to extracellular matrixes was found to be: ibandronate > NE-10244 (antiresorptive active pyridinium analog of risedronate) > pamidronate > clodronate. BP did not affect [3H]thymidine incorporation by tumor cells, as assessed by a mitogenesis assay, indicating that BP did not exert any cytotoxic effect at concns. used to inhibit tumor cell adhesion. NE-58051, the inactive pyridylpropylidene analog of risedronate, had no inhibitory effect on tumor cell adhesion compared to that observed with its active counterpart NE-10244, suggesting that the mechanism of action of BP on tumor cells involved a stereospecific recognition step. Although **integrins** mediate cell-matrix interactions, BP recognition by tumor cells did not modulate cell surface **integrin** expression. In conclusion, our results provide evidence for a direct cellular effect of BP in preventing tumor cell adhesion to bone, suggesting that BPs may be useful agents for the prophylactic treatment of patients with cancer that is known to preferentially metastasize to bone.

ST **bisphosphonate** tumor adhesion bone extracellular matrix; antitumor **bisphosphonate** bone metastasis

IT **Bone**
Cell adhesion
Extracellular matrix
(**bisphosphonates** inhibition of prostate and breast carcinoma cell adhesion to unmineralized and mineralized bone extracellular matrixes)

IT Mammary gland
Prostate gland
(carcinoma, inhibitors; **bisphosphonates** inhibition of prostate and breast carcinoma cell adhesion to unmineralized and mineralized bone extracellular matrixes)

IT **Osteoblast**
(extracellular matrix; **bisphosphonates** inhibition of prostate and breast carcinoma cell adhesion to unmineralized and mineralized bone extracellular matrixes)

IT Antitumor agents
(mammary gland carcinoma; **bisphosphonates** inhibition of prostate and breast carcinoma cell adhesion to unmineralized and mineralized bone extracellular matrixes)

IT Antitumor agents
(prostate carcinoma; **bisphosphonates** inhibition of prostate and breast carcinoma cell adhesion to unmineralized and mineralized bone extracellular matrixes)

IT **104261-69-0**, NE 58051
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**bisphosphonates** inhibition of prostate and breast carcinoma cell adhesion to unmineralized and mineralized bone extracellular matrixes)

IT **10596-23-3 40391-99-9 114084-78-5**, Ibandronate
197313-76-1, NE 10244
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonates** inhibition of prostate and breast carcinoma cell adhesion to unmineralized and mineralized bone extracellular matrixes)

RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE
(1) Abbadia, Z; FEBS Lett 1993, V335, P161 HCAPLUS
(2) Clezardin, P; Cancer Res 1991, V51, P2621 HCAPLUS
(3) Clezardin, P; Eur J Biochem 1989, V181, P721 HCAPLUS
(4) Diel, I; Proc Am Soc Clin Oncol 1997, V16, P130a
(5) Ebetino, F; Bisphosphonates on bones 1995, P139 HCAPLUS
(6) Galasko, C; Skeletal metastases 1986
(7) Haas, T; Curr Opin Cell Biol 1994, V6, P656 HCAPLUS
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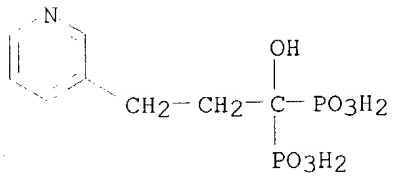
(9) Kanis, J; Bone 1996, V19, P663 HCAPLUS
(10) Kirk, M; J Bone Miner Res 1995, V10, P1203 HCAPLUS
(11) Rodan, G; J Clin Invest 1996, V97, P2692 HCAPLUS
(12) Sasaki, A; Cancer Res 1995, V55, P3551 HCAPLUS
(13) van der Pluijm, G; J Clin Invest 1996, V98, P698 HCAPLUS
(14) Yoneda, T; Int J Oncol 1996, V9, P103

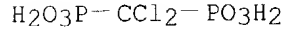
IT **104261-69-0**, NE 58051
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**bisphosphonates** inhibition of prostate and breast carcinoma cell adhesion to unmineralized and mineralized bone extracellular matrixes)

RN 104261-69-0 HCAPLUS
CN Phosphonic acid, [1-hydroxy-3-(3-pyridinyl)propylidene]bis- (9CI) (CA INDEX NAME)

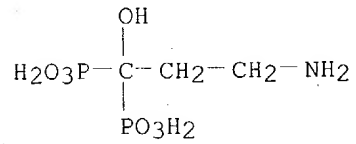


IT **10596-23-3 40391-99-9 114084-78-5**, Ibandronate
197313-76-1, NE 10244
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonates** inhibition of prostate and breast carcinoma cell adhesion to unmineralized and mineralized bone extracellular matrixes)

RN 10596-23-3 HCAPLUS
CN Phosphonic acid, (dichloromethylene)bis- (9CI) (CA INDEX NAME)

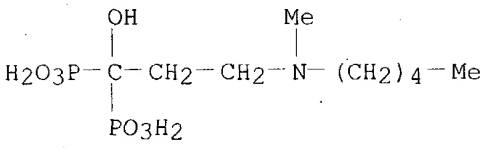


RN 40391-99-9 HCAPLUS
CN Phosphonic acid, (3-amino-1-hydroxypropylidene)bis- (9CI) (CA INDEX NAME)

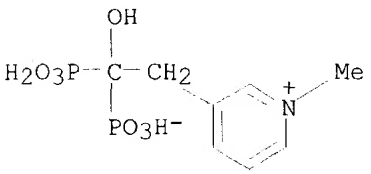


RN 114084-78-5 HCAPLUS
CN Phosphonic acid, [1-hydroxy-3-(methylpentylamino)propylidene]bis- (9CI)

(CA INDEX NAME)



RN 197313-76-1 HCAPLUS
CN Pyridinium, 3-(2-hydroxy-2,2-diphosphonoethyl)-1-methyl-, inner salt, disodium salt (9CI) (CA INDEX NAME)



●2 Na

L94 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1997:593792** HCAPLUS
DN **127:242709**
ED Entered STN: 17 Sep 1997
TI **Thalidomide** may impede cell migration in primates by down-regulating **integrin** β-chains: potential therapeutic utility in solid malignancies, proliferative retinopathy, inflammatory disorders, neointimal hyperplasia, and osteoporosis
AU Mccarty, M. F.
CS Nutrition 21, San Diego, CA, 92109, USA
SO Medical Hypotheses (**1997**), 49(2), 123-131
CODEN: MEHYDY; ISSN: 0306-9877
PB Churchill Livingstone
DT Journal; General Review
LA English
CC 1-0 (**Pharmacology**)
AB A review with 108 refs. A growing number of human inflammatory disorders are reported to respond to treatment with **thalidomide**, and recently this drug has been shown to inhibit angiogenesis in the rabbit, in doses which can elicit teratogenicity in this species. Studies in marmosets and humans indicate that **thalidomide**, and a teratogenic analog, decrease the expression of β **integrin** subunits, most notably β3 and the β2 produced by leukocytes. Since **integrins** are crucial for cell-matrix interactions, and the β2 **integrins** of leukocytes mediate adhesion to endothelium, it is reasonable to postulate that **thalidomide** inhibits cell migration in susceptible species, and that this accounts for its anti-inflammatory, anti-angiogenic, and teratogenic activity. This perspective suggests that **thalidomide** will show utility in the prevention or treatment of a wide range of disorders, including solid tumors, proliferative retinopathies, many inflammatory diseases, neointimal hyperplasia, and osteoporosis. It is likely that dietary fish oil - as well as selective inhibitors of urokinase, when and if they become clin. available - will complement the efficacy of

thalidomide in most if not all of these applications.

ST review **thalidomide** cell migration beta **integrin**; antitumor antiinflammatory antiangiogenic osteoporosis **thalidomide** review; retinopathy teratogen **thalidomide** fish oil review

IT Fats and Glyceridic oils, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fish; **thalidomide** effect on cell migration: down-regulation of β- **integrins** and potential therapeutic use in solid malignancies, proliferative retinopathy, inflammatory disorders, neointimal hyperplasia, and osteoporosis)

IT Eye, disease
(retinopathy; **thalidomide** effect on cell migration: down-regulation of β- **integrins** and potential therapeutic use in solid malignancies, proliferative retinopathy, inflammatory disorders, neointimal hyperplasia, and osteoporosis)

IT Angiogenesis inhibitors
Anti-inflammatory agents
Antitumor agents
Teratogens
(**thalidomide** effect on cell migration: down-regulation of β- **integrins** and potential therapeutic use in solid malignancies, proliferative retinopathy, inflammatory disorders, neointimal hyperplasia, and osteoporosis)

IT **Osteoporosis**
(therapeutic agents; **thalidomide** effect on cell migration: down-regulation of β- **integrins** and potential therapeutic use in solid malignancies, proliferative retinopathy, inflammatory disorders, neointimal hyperplasia, and osteoporosis)

IT **Integrins**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(β2; **thalidomide** effect on cell migration: down-regulation of β- **integrins** and potential therapeutic use in solid malignancies, proliferative retinopathy, inflammatory disorders, neointimal hyperplasia, and osteoporosis)

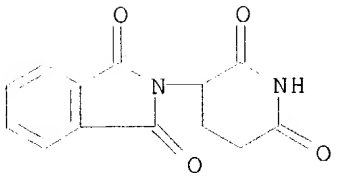
IT **Integrins**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(β3; **thalidomide** effect on cell migration: down-regulation of β- **integrins** and potential therapeutic use in solid malignancies, proliferative retinopathy, inflammatory disorders, neointimal hyperplasia, and osteoporosis)

IT **50-35-1, Thalidomide**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**thalidomide** effect on cell migration: down-regulation of β- **integrins** and potential therapeutic use in solid malignancies, proliferative retinopathy, inflammatory disorders, neointimal hyperplasia, and osteoporosis)

IT **50-35-1, Thalidomide**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**thalidomide** effect on cell migration: down-regulation of β- **integrins** and potential therapeutic use in solid malignancies, proliferative retinopathy, inflammatory disorders, neointimal hyperplasia, and osteoporosis)

RN 50-35-1 HCAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L94 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:756546 HCAPLUS
DN 126:17804
ED Entered STN: 26 Dec 1996
TI Human antibodies derived from immunized xenomice
IN Kucherlapati, Raju; Jakobovits, Aya; Klapholz, Sue; Brenner, Daniel G.; Capon, Daniel J.
PA Cell Genesys, Inc., USA
SO PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N015-00
CC 15-3 (**Immunochemistry**)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9634096	A1	19961031	WO 1995-US5500	19950428 <--
	W: AU, CA, FI, HU, JP, KR, NO, NZ				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2219486	AA	19961031	CA 1995-2219486	19950428 <--
	AU 9524668	A1	19961118	AU 1995-24668	19950428 <--
	EP 823941	A1	19980218	EP 1995-918935	19950428 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
	JP 11505107	T2	19990518	JP 1995-532463	19950428 <--
PRAI	WO 1995-US5500		19950428 <--		

AB Antibodies with fully human variable regions against a specific antigen can be prepared by administering the antigen to a transgenic animal which has been modified to produce such antibodies in response to antigenic challenge, but whose endogenous loci have been disabled. Various subsequent manipulations can be performed to obtain either antibodies per se or analogs thereof.

ST human antibody Ig xenomice therapeutic
IT Interleukin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(12; human antibodies derived from immunized xenomice)
IT Antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(A7; human antibodies derived from immunized xenomice)
IT Antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(B7.3; human antibodies derived from immunized xenomice)
IT Glycoproteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(B; human antibodies derived from immunized xenomice)
IT CD antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CD27; human antibodies derived from immunized xenomice)
IT Antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CD29 ligand; human antibodies derived from immunized xenomice)
IT Antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CD30 ligand; human antibodies derived from immunized xenomice)

IT Glycoproteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CD40-L (antigen CD40 ligand); human antibodies derived from immunized xenomice)
IT CD antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CD6; human antibodies derived from immunized xenomice)
IT CD antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CD72; human antibodies derived from immunized xenomice)
IT CD antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CDw52; human antibodies derived from immunized xenomice)
IT Envelope proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(E glycoprotein; human antibodies derived from immunized xenomice)
IT Selectins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(E-; human antibodies derived from immunized xenomice)
IT Immunoglobulins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(E; human antibodies derived from immunized xenomice)
IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ECP (eosinophil cationic protein); human antibodies derived from immunized xenomice)
IT Cytokines
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Groα; human antibodies derived from immunized xenomice)
IT Cytokines
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Groβ; human antibodies derived from immunized xenomice)
IT Glycoproteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(H-CAM (homing cell adhesion mol.); human antibodies derived from immunized xenomice)
IT Cell adhesion molecules
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ICAM-1 (intercellular adhesion mol. 1); human antibodies derived from immunized xenomice)
IT Cell adhesion molecules
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ICAM-2 (intercellular adhesion mol. 2); human antibodies derived from immunized xenomice)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Ig.; human antibodies derived from immunized xenomice)
IT Immunoglobulin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(IgE type I; human antibodies derived from immunized xenomice)
IT Immunoglobulin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(IgE type II; human antibodies derived from immunized xenomice)
IT Immunoglobulin receptors
Immunoglobulin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(IgE; human antibodies derived from immunized xenomice)
IT Selectins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(L-; human antibodies derived from immunized xenomice)
IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(LMP-1; human antibodies derived from immunized xenomice)

IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(LMP-2 (latent-infection membrane protein 2); human antibodies derived from immunized xenomice)
IT Blood-group substances
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Leb, synthetic; human antibodies derived from immunized xenomice)
IT Blood-group substances
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Ley; human antibodies derived from immunized xenomice)
IT Allergens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Lol p I (Lolium perenne, I); human antibodies derived from immunized xenomice)
IT Cytokines
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(MBP (major basic protein); human antibodies derived from immunized xenomice)
IT Histocompatibility antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(MHC (major histocompatibility complex), class I; human antibodies derived from immunized xenomice)
IT Histocompatibility antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(MHC (major histocompatibility complex), class II; human antibodies derived from immunized xenomice)
IT Selectins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(P-; human antibodies derived from immunized xenomice)
IT Chemokines
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(PF4; human antibodies derived from immunized xenomice)
IT Skin, disease
(Paget disease; human antibodies derived from immunized xenomice)
IT **Bone, disease**
(Paget's; human antibodies derived from immunized xenomice)
IT Arthritis
Arthritis
Arthritis
(Reiter's syndrome; human antibodies derived from immunized xenomice)
IT Blood-group substances
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Rh; human antibodies derived from immunized xenomice)
IT Cell adhesion molecules
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(VCAM-1; human antibodies derived from immunized xenomice)
IT Respiratory distress syndrome
(adult; human antibodies derived from immunized xenomice)
IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(amadori; human antibodies derived from immunized xenomice)
IT Dermatophagoides
Leukocyte
(antigen; human antibodies derived from immunized xenomice)
IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antigens CD11a; human antibodies derived from immunized xenomice)
IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antigens CD11b; human antibodies derived from immunized xenomice)
IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antigens CD11c; human antibodies derived from immunized xenomice)

IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antigens Mac-1 (macrophage 1); human antibodies derived from immunized xenomice)
IT Thyroid gland, disease
(autoimmune thyroiditis; human antibodies derived from immunized xenomice)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(c-erbB2, products; human antibodies derived from immunized xenomice)
IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cholesterol ester-exchanging; human antibodies derived from immunized xenomice)
IT Mammary gland
Reproductive tract
(disease, Paget; human antibodies derived from immunized xenomice)
IT Sialoglycoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(endosialins; human antibodies derived from immunized xenomice)
IT Toxins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(endotoxins; human antibodies derived from immunized xenomice)
IT Glycoproteins, specific or class
RL: BSU (Biological study, unclassified); BI0L (Biological study)
(gH; human antibodies derived from immunized xenomice)
IT Glycoproteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gcIII; human antibodies derived from immunized xenomice)
IT Kidney, disease
(glomerulonephritis; human antibodies derived from immunized xenomice)
IT Lipids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(glycated; human antibodies derived from immunized xenomice)
IT Glycoproteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gp39; human antibodies derived from immunized xenomice)
IT Transplant and Transplantation
(graft-vs.-host reaction; human antibodies derived from immunized xenomice)
IT Myelin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(growth inhibitor associated with; human antibodies derived from immunized xenomice)
IT Animal cell
Animal cell line
Asthma
Autoimmune disease
B cell (lymphocyte)
Behcet's syndrome
Cachexia
Cytomegalovirus
Dermatomyositis
Diagnosis
Graves' disease
Hepatitis virus
Human herpesvirus
Human herpesvirus 3
Human herpesvirus 4
Human immunodeficiency virus 1
Human papillomavirus
Multiple myeloma
Multiple sclerosis

Myasthenia gravis
Osteoporosis
Pseudomonas
Psoriasis
Respiratory syncytial virus
Rheumatoid arthritis
Sjogren's syndrome
Therapy
(human antibodies derived from immunized xenomice)

IT Antibodies
Immunoglobulins
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(human antibodies derived from immunized xenomice)

IT Allergens
Antigens
Blood-coagulation factors
CD14 (antigen)
CD19 (antigen)
CD2 (antigen)
CD20 (antigen)
CD22 (antigen)
CD28 (antigen)
CD3 (antigen)
CD30 (antigen)
CD4 (antigen)
CD40 (antigen)
CD44 (antigen)
CD45 (antigen)
CD5 (antigen)
CD56 (antigen)
CD69 (antigen)
CD7 (antigen)
CD8 (antigen)
CD80 (antigen)
CD86 (antigen)
CTLA-4 (antigen)
Carcinoembryonic antigen
Cell adhesion molecules
Chemokines
Enzymes, biological studies
Epidermal growth factor receptors
Erythropoietin receptors
Fas antigen
Fibrinogens
Fibrins
Fibroblast growth factor receptors
Granulocyte colony-stimulating factor receptors
Growth factor receptors
Growth factors, animal
Hematopoietin receptors
Histocompatibility antigens
Immunoglobulin receptors
Interferon receptors
Interleukin 1
Interleukin 1 receptors
Interleukin 10
Interleukin 11
Interleukin 12
Interleukin 13
Interleukin 14
Interleukin 15
Interleukin 2

Interleukin 2 receptors
Interleukin 3
Interleukin 3 receptors
Interleukin 4
Interleukin 4 receptors
Interleukin 5
Interleukin 5 receptors
Interleukin 6
Interleukin 6 receptors
Interleukin 7
Interleukin 7 receptors
Interleukin 8
Interleukin 8 receptors
Interleukin 9
Interleukin receptors
Interleukins
LFA-1 (antigen)
LFA-3 (antigen)
Macrophage inflammatory protein 1α
Monocyte chemoattractant protein-1
Mucins
Neutrophil-activating peptide-2
Osteopontin
P-glycoproteins
Platelet-derived growth factor receptors
Platelet-derived growth factors
RANTES (chemokine)
TCR (T cell receptors)
Thyrotropin receptors
Toxins
Tumor necrosis factor receptors
Tumor necrosis factors
Vascular endothelial growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(human antibodies derived from immunized xenomice)

IT Parathyroid hormone receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(humoral hypercalcemic factor; human antibodies derived from immunized xenomice)

IT Reperfusion
(injury; human antibodies derived from immunized xenomice)

IT Diabetes mellitus
(insulin-dependent; human antibodies derived from immunized xenomice)

IT Interleukin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(interleukin 10 receptors; human antibodies derived from immunized xenomice)

IT Interleukin receptors
Interleukin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(interleukin 11; human antibodies derived from immunized xenomice)

IT Interleukin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(interleukin 12; human antibodies derived from immunized xenomice)

IT Interleukin receptors
Interleukin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(interleukin 13; human antibodies derived from immunized xenomice)

IT Receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(interleukin 14; human antibodies derived from immunized xenomice)

IT Interleukin receptors
Interleukin receptors

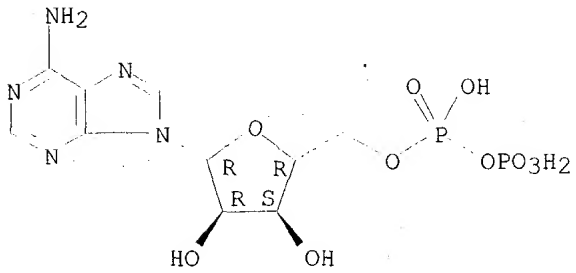
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**interleukin 15**; human antibodies derived from immunized xenomice)
IT Interleukin receptors
Interleukin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(interleukin 9; human antibodies derived from immunized xenomice)
IT Selectins
Selectins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ligands; human antibodies derived from immunized xenomice)
IT Lipoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(low-d., oxidized; human antibodies derived from immunized xenomice)
IT Neoplasm
(metastasis; human antibodies derived from immunized xenomice)
IT Connective tissue
(mixed connective tissue disease; human antibodies derived from immunized xenomice)
IT Antibodies
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(monoclonal; human antibodies derived from immunized xenomice)
IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p150,95 antigen; human antibodies derived from immunized xenomice)
IT Antibodies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pANCA or perinuclear antineutrophil cytoplasm antibodies; human antibodies derived from immunized xenomice)
IT Skin, disease
(pemphigus; human antibodies derived from immunized xenomice)
IT Muscle, disease
(polymyositis; human antibodies derived from immunized xenomice)
IT Virus
(protein; human antibodies derived from immunized xenomice)
IT DNA
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(recombinant; human antibodies derived from immunized xenomice)
IT Transplant and Transplantation
(rejection; human antibodies derived from immunized xenomice)
IT Kidney, neoplasm
(renal cell carcinoma; human antibodies derived from immunized xenomice)
IT Ischemia
(reperfusion; human antibodies derived from immunized xenomice)
IT Connective tissue
(scleroderma; human antibodies derived from immunized xenomice)
IT Ligands
Ligands
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(selectin; human antibodies derived from immunized xenomice)
IT Shock (circulatory collapse)
(septic; human antibodies derived from immunized xenomice)
IT Venoms
Venoms
(snake; human antibodies derived from immunized xenomice)
IT Antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(surface, hepatitis virus; human antibodies derived from immunized xenomice)
IT Lupus erythematosus

(systemic; human antibodies derived from immunized xenomice)
IT Toxins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tetanus; human antibodies derived from immunized xenomice)
IT Antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tumor-associated; human antibodies derived from immunized xenomice)
IT Collagens, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type IV; human antibodies derived from immunized xenomice)
IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(uropontins; human antibodies derived from immunized xenomice)
IT Bee
(venom; human antibodies derived from immunized xenomice)
IT Proteins, general, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(viral; human antibodies derived from immunized xenomice)
IT Mouse
(xeno-; human antibodies derived from immunized xenomice)
IT Interferon receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α-interferon; human antibodies derived from immunized xenomice)
IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α1β1; human antibodies derived from immunized xenomice)
IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α2β1; human antibodies derived from immunized xenomice)
IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α3β1; human antibodies derived from immunized xenomice)
IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α **4β 1**; human
antibodies derived from immunized xenomice)
IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α5β1; human antibodies derived from immunized xenomice)
IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α6β1; human antibodies derived from immunized xenomice)
IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β-; human antibodies derived from immunized xenomice)
IT Transforming growth factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β-transforming growth factor; human antibodies derived from
immunized xenomice)
IT Interferon receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β; human antibodies derived from immunized xenomice)
IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β1; human antibodies derived from immunized xenomice)
IT **Integrins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β2; human antibodies derived from immunized xenomice)
IT Interferon receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ-interferon; human antibodies derived from immunized xenomice)
IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(γ; human antibodies derived from immunized xenomice)
IT 9002-71-5, TSH 9024-58-2, Glutamic acid decarboxylase 9054-63-1, Antigens, CD13 19600-01-2, Ganglioside GM2 53237-59-5, Urushiol 62010-37-1, Ganglioside GD3 62031-54-3, FGF 62229-50-9, EGF 80043-53-4, Gastrin releasing peptide 80295-43-8, Complement C3b 80295-54-1, Complement C5a 81669-70-7, Metalloprotease 82986-89-8, Complement C5b-9 92448-22-1, SLea 98603-84-0, SLex 116243-73-3, Endothelin 127464-60-2, Vascular endothelial growth factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(human antibodies derived from immunized xenomice)
IT 9002-64-6, PTH
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(proteins related to; human antibodies derived from immunized xenomice)

L94 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1994:555179 HCAPLUS
DN 121:155179
ED Entered STN: 01 Oct 1994
TI Mechanism of platelet aggregation induced by anti-human platelet monoclonal antibody APT4
AU Yu, Aixin; Li, Jiazeng; Lian, Junyi
CS Inst. Hematology, Chin. Acad. Med. Sci., Tianjin, 300020, Peop. Rep. China
SO Zhonghua Xueyexue Zazhi (**1994**), 15(3), 115-18
CODEN: CHTCD7; ISSN: 0253-2727
DT Journal
LA Chinese
CC 15-3 (**Immunochemistry**)
AB A monoclonal antibody designated APT4 was produced by fusion of mouse **myeloma** cells to spleen cells from a BALB/C mouse immunized with normal human platelets. APT4 IgG caused the aggregation of both PRP and washed platelets from normal subjects and a patient with Bernard Soulier's syndrome, but not those from two patients with the type 1 Glanzmann's thrombasthenia. No aggregation was observed when APT4 F(ab') 2 was used. SDS-PAGE of the immunoppts. of 125I labeled platelet membrane lysates by APT4 showed two protein bands corresponding to GPIIb and IIIa. In conclusion, APT4 bound to GPIIb-IIIa complex and induced aggregation requiring energy metabolism, calcium, Fc fragment of IgG and ADP release, but independent of thromboxane A2 formation.
ST monoclonal antibody platelet aggregation
IT Blood platelet
(monoclonal antibody to, platelet aggregation induced by, mechanism of)
IT Antibodies
RL: BIOL (Biological study)
(monoclonal, to platelets, platelet aggregation induced by, mechanism of)
IT **Integrins**
RL: BIOL (Biological study)
(αIIb, monoclonal antibody-induced platelet aggregation in relation to)
IT **Integrins**
RL: BIOL (Biological study)
(β3, monoclonal antibody-induced platelet aggregation in relation to)
IT **58-64-0**, ADP, biological studies 7440-70-2, Calcium, biological studies
RL: BIOL (Biological study)
(monoclonal antibody-induced platelet aggregation in relation to)
IT **58-64-0**, ADP, biological studies
RL: BIOL (Biological study)
(monoclonal antibody-induced platelet aggregation in relation to)
RN 58-64-0 HCAPLUS
CN Adenosine 5'-(trihydrogen diphosphate) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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=> d all tot l105

L105 ANSWER 1 OF 3 MEDLINE on STN DUPLICATE 1
AN 1999155345 MEDLINE
DN 99155345 PubMed ID: 10029595
TI Cell adhesion mediated drug resistance (CAM-DR): role of **integrins** and resistance to apoptosis in human myeloma cell lines.
AU Damiano J S; Cress A E; Hazlehurst L A; Shtil A A; Dalton W S
CS H. Lee. Moffitt Cancer Center, University of South Florida, Tampa, FL; and the Arizona Cancer Center, University of Arizona, Tucson, AZ.
NC CA 17094 (NCI)
SO BLOOD, **(1999 Mar 1)** 93 (5) 1658-67.
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199903
ED Entered STN: 19990326
Last Updated on STN: 19990326
Entered Medline: 19990318
AB **Integrin**-mediated adhesion influences cell survival and may prevent programmed cell death. Little is known about how drug-sensitive tumor cell lines survive initial exposures to cytotoxic drugs and eventually select for drug-resistant populations. Factors that allow for cell survival following acute cytotoxic drug exposure may differ from drug resistance mechanisms selected for by chronic drug exposure. We show here that drug-sensitive 8226 human myeloma cells, demonstrated to express both VLA-4 (alpha4beta1) and VLA-5 (alpha5beta1) **integrin** fibronectin (FN) receptors, are relatively resistant to the apoptotic effects of doxorubicin and **melphalan** when pre-adhered to FN and compared with cells grown in suspension. This cell adhesion mediated drug resistance, or CAM-DR, was not due to reduced drug accumulation or upregulation of anti-apoptotic Bcl-2 family members. As determined by flow cytometry, myeloma cell lines selected for drug resistance, with either doxorubicin or **melphalan**, overexpress VLA-4. Functional assays revealed a significant increase in alpha4-mediated cell adhesion in both drug-resistant variants compared with the drug-sensitive parent line. When removed from selection pressure, drug-resistant cell lines reverted to a drug sensitive and alpha4-low phenotype. Whether VLA-4-mediated FN adhesion offers a survival advantage over VLA-5-mediated adhesion remains

to be determined. In conclusion, we have demonstrated that FN-mediated adhesion confers a survival advantage for myeloma cells acutely exposed to cytotoxic drugs by inhibiting drug-induced apoptosis. This finding may explain how some cells survive initial drug exposure and eventually express classical mechanisms of drug resistance such as MDR1 overexpression.

CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
Antineoplastic Agents
Apoptosis: DE, drug effects
*Apoptosis: GE, genetics
Cell Adhesion: GE, genetics
Doxorubicin: PD, pharmacology
*Drug Resistance, Neoplasm: GE, genetics
Fibronectins: ME, metabolism
*Gene Expression Regulation, Neoplastic
***Integrins: GE, genetics**
Melphalan: PD, pharmacology
*Multiple Myeloma: GE, genetics
Multiple Myeloma: ME, metabolism
*Multiple Myeloma: PA, pathology
Tumor Cells, Cultured

RN **148-82-3 (Melphalan)**; 23214-92-8 (Doxorubicin)

CN 0 (Antineoplastic Agents); 0 (Fibronectins); 0 (**Integrins**)

L105 ANSWER 2 OF 3 MEDLINE on STN

AN 95276269 MEDLINE

DN 95276269 PubMed ID: 7538823

TI Expression of adhesion molecules on CD34+ cells: CD34+ L-selectin+ cells predict a rapid platelet recovery after peripheral blood stem cell transplantation.

AU Dercksen M W; Gerritsen W R; Rodenhuis S; Dirkson M K; Slaper-Cortenbach I C; Schaasberg W P; Pinedo H M; von dem Borne A E; van der Schoot C E

CS European Cancer Centre, Amsterdam, The Netherlands.

SO BLOOD, **(1995 Jun 1)** 85 (11) 3313-9.
Journal code: 7603509. ISSN: 0006-4971.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 199506

ED Entered STN: 19950707
Last Updated on STN: 19960129
Entered Medline: 19950623

AB Adhesion molecules play a role in the migration of hematopoietic progenitor cells and regulation of hematopoiesis. To study whether the mobilization process is associated with changes in expression of adhesion molecules, the expression of CD31, CD44, L-selectin, sialyl Lewisx, beta 1 **integrins** very late antigen 4 (VLA-4) and VLA-5, and beta 2 **integrins** lymphocyte function-associated 1 and Mac-1 was measured on either bone marrow (BM) CD34+ cells or on peripheral blood CD34+ cells mobilized with a combination of granulocyte colony-stimulating factor (G-CSF) and chemotherapy. beta 1 **integrin** VLA-4 was expressed at a significantly lower concentration on peripheral blood progenitor cells than on BM CD34+ cells, procured either during steady-state hematopoiesis or at the time of leukocytapheresis. No differences in the level of expression were found for the other adhesion molecules. To obtain insight in which adhesion molecules may participate in the homing of peripheral blood stem cells (PBSCs), the number of CD34+ cells expressing these adhesion molecules present in leukocytapheresis material was quantified and correlated with hematopoietic recovery after intensive chemotherapy in 27 patients. The number of CD34+ cells in the subset defined by L-selectin expression correlated significantly better with time to platelet recovery after PBSC transplantation ($r = -.86$) than did the total

number of CD34+ cells (r = -.55). Statistical analysis of the relationship between the number of CD34+L-selectin+ cells and platelet recovery resulted in a threshold value for rapid platelet recovery of 2.1 x 10(6) CD34+ L-selectin+ cells/kg. A rapid platelet recovery (< or = 14 days) was observed in 13 of 15 patients who received > or = 2.1 x 10(6) CD34+ L-selectin+ cells/kg (median, 11 days; range, 7 to 16 days), whereas 10 of 12 patients who received less double positive cells had a relative slow platelet recovery (median, 20 days; range, 13 to 37 days). The L-selectin+ subpopulation of CD34+ cells also correlated better with time to neutrophil recovery (r = -.70) than did the total number of reinfused CD34+ cells (r = -.51). However, this latter difference failed to reach statistical significance. This study suggests that L-selectin is involved in the homing of CD34+ cells after PBSC transplantation.

CT Check Tags: Female; Human; Male
Adult
Antigens, CD: AN, analysis
Antigens, CD34
Antineoplastic Combined Chemotherapy Protocols: PD, pharmacology
Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use
Biological Markers
Bone Marrow: DE, drug effects
Bone Marrow Cells
Carboplatin: AD, administration & dosage
Carmustine: AD, administration & dosage
Cell Adhesion Molecules: BI, biosynthesis
*Cell Adhesion Molecules: PH, physiology
Cell Movement: PH, physiology
Combined Modality Therapy
Cyclophosphamide: AD, administration & dosage
Cytarabine: AD, administration & dosage
Epirubicin: AD, administration & dosage
Etoposide: AD, administration & dosage
Fluorouracil: AD, administration & dosage
Gene Expression
Granulocyte Colony-Stimulating Factor: PD, pharmacology
Hematopoiesis
*Hematopoietic Stem Cell Transplantation
Hematopoietic Stem Cells: CY, cytology
*Hematopoietic Stem Cells: ME, metabolism
Ifosfamide: AD, administration & dosage
L-Selectin
Leukocyte Count
Melphalan: AD, administration & dosage
Middle Age
Neoplasms: DT, drug therapy
Neoplasms: TH, therapy
Neutrophils
*Platelet Count
Podophyllotoxin: AD, administration & dosage
Receptors, Very Late Antigen: BI, biosynthesis
*Receptors, Very Late Antigen: PH, physiology
Thiotepa: AD, administration & dosage

RN 126880-86-2 (L-Selectin); 143011-72-7 (Granulocyte Colony-Stimulating Factor); 147-94-4 (Cytarabine); **148-82-3 (Melphalan)**; 154-93-8 (Carmustine); 33419-42-0 (Etoposide); 3778-73-2 (Ifosfamide); 41575-94-4 (Carboplatin); 50-18-0 (Cyclophosphamide); 51-21-8 (Fluorouracil); 518-28-5 (Podophyllotoxin); 52-24-4 (Thiotepa); 56420-45-2 (Epirubicin)

CN 0 (Antigens, CD); 0 (Antigens, CD34); 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (BEAM protocol); 0 (Biological Markers); 0 (Cell Adhesion Molecules); 0 (Receptors, Very Late Antigen)

L105 ANSWER 3 OF 3 EMBASE
on STN

AN 96286625 EMBASE
DN 1996286625
TI [The results of a randomised study in the treatment of multiple **myeloma**].
VYSLEDKY RANDOMIZOVANEJ STUDIE V ZAVISLOSTI OD POSTUPU LIECBY PRI MNOHOPOCETNOM MYELOME.
AU Sakalova A.; Desser L.; Gazova S.; Prummerova M.; Chabronova I.; Mistrik M.; Hrubisko M.; Holomanova D.; Hapalova J.
CS Klinika Hematologie/Transfuziologie, Fakultna Nemocnica,Bratislava, Slovakia
SO Klinicka Onkologie, (1996) 9/4 (130-134).
ISSN: 0862-495X CODEN: KLONEU
CY Czech Republic
DT Journal; Article
FS 013 Dermatology and Venereology
016 Cancer
037 Drug Literature Index
LA Slovak
SL English; Slovak
AB The authors in this study are continuing in their long term experience in the treatment of multiple **myeloma** by polychemotherapy according to protocol VMCP/MOCCA. Since 1990 a randomised group was created - only chemotherapy was given in the first group of 96 patients, in the second one chemotherapy combined with proteolytical enzymes was used (Wobe Mugos). The enzymes are the biological response modifiers, and as shown in the frequency and survival curves, the medial survival has lengthened from 20 to 47 months. The prolongation of survival is significant in the stage II patients and can be explained by tumor mass reduction, decrease cytokine activity, but mostly by decrease of infectious complications. The laboratory tests have shown a significant decrease of B2M, serum soluble TNF receptors and a decrease of the cellular membrane receptor density (CD38, **Integrins**, CD44, CD54, CD56). The overall survival of 198 patients in the chemotherapy group is more than 71 months and in the immunochemotherapy more than 85 months in 70% of patients in follow up.
CT Medical Descriptors:
***multiple myeloma: DT, drug therapy**
article
cancer chemotherapy
cancer regression
cancer survival
clinical trial
human
major clinical study
randomized controlled trial
Drug Descriptors:
*antineoplastic agent: CT, clinical trial
*antineoplastic agent: DT, drug therapy
*wobe mugos: CT, clinical trial
*wobe mugos: DT, drug therapy
cyclophosphamide: DT, drug therapy
cyclophosphamide: CT, clinical trial
melphalan: CT, clinical trial
melphalan: DT, drug therapy
membrane receptor: EC, endogenous compound
methylprednisolone: CT, clinical trial
methylprednisolone: DT, drug therapy
prednisone: DT, drug therapy
prednisone: CT, clinical trial
vincristine: DT, drug therapy
vincristine: CT, clinical trial
unclassified drug
RN (wobe mugos) 60098-82-0; (cyclophosphamide) 50-18-0; (**melphalan**) **148-82-3**; (methylprednisolone) 6923-42-8, 83-43-2; (prednisone)

53-03-2; (vincristine) 57-22-7
CN **Alkeran**; Urbason; Wobe mugos

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FILE LAST UPDATED: 16 DEC 2003 <20031216/UP>
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L127 ANSWER 1 OF 2 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN
AN **2001-582112** [65] WPIX
DNC **C2001-172606**
TI Use of **bisphosphonate** compounds for inhibiting cell adhesion
mediated drug resistance and enhancing efficacy of chemotherapeutic and/or
radiation treatments.
DC B05
IN DALTON, W S; DAMIANO, J S
PA (UYSF-N) UNIV SOUTH FLORIDA; (DALT-I) DALTON W S; (DAMI-I) DAMIANO J S
CYC 94
PI WO 2001064207 A2 20010907 (200165)* EN 77p A61K031-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001039953 A 20010912 (200204) A61K031-00
US 2003004140 A1 20030102 (200305) A61K031-66
ADT WO 2001064207 A2 WO 2001-US6466 20010301; AU 2001039953 A AU 2001-39953
20010301; US 2003004140 A1 Provisional US 2000-186199P 20000301, Cont of
US 2001-795474 20010301, US 2001-24018 20011221
FDT AU 2001039953 A Based on WO 2001064207
PRAI US 2000-186199P 20000301; US 2001-795474 20010301; US 2001-24018
20011221
IC ICM A61K031-00; A61K031-66
ICS A61N005-00
AB WO 200164207 A UPAB: 20011108

NOVELTY - The use of **bisphosphonate** compounds for inhibiting cell adhesion mediated drug resistance and enhancing efficacy of chemotherapy and/or radiation therapy in the treatment of cancer, is new.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - Inhibit **integrin**-mediated cell adhesion.

The effect of clodronate on adhesion of 8226 **myeloma** cells was determined. Cells were incubated in the presence and absence of 100 mu M clodronate for 1.5 hours, then plated onto collagen-coated 6-well plates. After 2 hours, etoposide (50 mu M) was added. After 2 hours the adhered cells were washed. Non-adherent cells were aspirated, washed and resuspended in drug free medium, and returned to their respective wells together with adherent cells. Apoptosis was measured 24 hours later. Results for % etoposide specific apoptosis were, for the suspension about 45% in the absence of clodronate and about 50% in the presence of clodronate; and for collagen about 28% in the absence of clodronate and about 49% in the presence of clodronate;

USE - For treating cancer, e.g. **myeloma** or **multiple myeloma**.

Dwg.0/28

FS CPI
FA AB; DCN
MC CPI: B05-B01E; B05-B01G; B14-H01
TECH UPTX: 20011108

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compounds: The **bisphosphonate** compound is etidronate, clodronate, pamidronate and/or zoledronate.

ABEX UPTX: 20011108

WIDER DISCLOSURE - Cancer cell interaction with the extracellular matrix, including fibronectin and collagen, prevents cell death induced by cytotoxic drugs and radiation. Also, **integrin**-mediated adhesion, including alpha4beta1 and alpha5beta1 for fibronectin and alpha2beta1 for collagen, prevents both drug and radiation induced cancer cell death.

ADMINISTRATION - The **bisphosphonate** compound is preferably administered prior to administration of chemotherapy and/or radiation therapy.

L127 ANSWER 2 OF 2 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN
AN **2000-271253** [23] WPIX
DNC **C2000-082763**
TI Treating multiple **myeloma** and **myeloma**-induced bone reabsorption using antagonists of the alpha4/alpha4 integrin ligand pathway.
DC B04 D16
IN **MUNDY, G R; YONEDA, T**; TOSHIYUKI, Y
PA (BIOJ) BIOGEN INC; (TEXA) UNIV TEXAS SYSTEM; (MUND-I) MUNDY G R; (YONE-I) YONEDA T
CYC 84
PI WO 2000015247 A2 20000323 (200023)* EN 54p A61K038-17
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
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AU 9962486 A 20000403 (200034) A61K038-17
NO 2001001244 A 20010514 (200134) A61K000-00
BR 9913705 A 20010605 (200138) A61K038-17
EP 1113810 A2 20010711 (200140) EN A61K038-17
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CZ 2001000916 A3 20010815 (200157) A61K038-17

SK 2001000605	A3	20011203	(200203)		A61K038-17
CN 1321091	A	20011107	(200216)		A61K038-17
KR 2001085793	A	20010907	(200218)		A61K039-395
US 2002022028	A1	20020221	(200221)		A61K039-395
HU 2001003630	A2	20020128	(200222)		A61K038-17
US 2002041874	A1	20020411	(200227)		A61K039-395
JP 2002524529	W	20020806	(200266)	64p	A61K045-00
US 2002159998	A1	20021031	(200274)		A61K039-395
ZA 2001002032	A	20030129	(200314)	69p	A61K000-00
AU 757873	B	20030306	(200324)		A61K038-17
NZ 511062	A	20030429	(200334)		A61K038-17
MX 2001002670	A1	20020301	(200362)		A61K038-17

ADT WO 2000015247 A2 WO 1999-US21170 19990913; AU 9962486 A AU 1999-62486 19990913; NO 2001001244 A WO 1999-US21170 19990913, NO 2001-1244 20010312; BR 9913705 A BR 1999-13705 19990913, WO 1999-US21170 19990913; EP 1113810 A2 EP 1999-949656 19990913, WO 1999-US21170 19990913; CZ 2001000916 A3 WO 1999-US21170 19990913, CZ 2001-916 19990913; SK 2001000605 A3 WO 1999-US21170 19990913, SK 2001-605 19990913; CN 1321091 A CN 1999-810904 19990913; KR 2001085793 A KR 2001-703274 20010314; US 2002022028 A1 Provisional US 1998-100182P 19980914, Cont of WO 1999-US21170 19990913, US 2001-805840 20010313; HU 2001003630 A2 WO 1999-US21170 19990913, HU 2001-3630 19990913; US 2002041874 A1 Provisional US 1998-100182P 19980914, Cont of WO 1999-US21170 19990913, CIP of US 2001-805840 20010313, US 2001-943659 20010831; JP 2002524529 W WO 1999-US21170 19990913, JP 2000-569831 19990913; US 2002159998 A1 Provisional US 1998-100182P 19980914, Cont of WO 1999-US21170 19990913, CIP of US 2001-805840 20010313, CIP of US 2001-943659 20010831, US 2002-86217 20020221; ZA 2001002032 A ZA 2001-2032 20010312; AU 757873 B AU 1999-62486 19990913; NZ 511062 A NZ 1999-511062 19990913, WO 1999-US21170 19990913; MX 2001002670 A1 WO 1999-US21170 19990913, MX 2001-2670 20010314

FDT AU 9962486 A Based on WO 2000015247; BR 9913705 A Based on WO 2000015247; EP 1113810 A2 Based on WO 2000015247; CZ 2001000916 A3 Based on WO 2000015247; SK 2001000605 A3 Based on WO 2000015247; HU 2001003630 A2 Based on WO 2000015247; JP 2002524529 W Based on WO 2000015247; AU 757873 B Previous Publ. AU 9962486, Based on WO 2000015247; NZ 511062 A Based on WO 2000015247; MX 2001002670 A1 Based on WO 2000015247

PRAI US 1998-100182P 19980914; US 2001-805840 20010313; US 2001-943659 20010831; US 2002-86217 20020221

IC ICM A61K000-00; A61K038-17; A61K039-395; A61K045-00
ICS A61P019-00; A61P035-00; C07K016-18; C12N015-09

ICA C07K014-705; C07K016-28

ICI C07K014:705, C07K016-28

AB WO 200015247 A UPAB: 20000516

NOVELTY - Methods for treating multiple **myeloma** and **myeloma**-induced bone reabsorptions, comprising using integrin antagonists to disrupt the alpha4 integrin/alpha4 integrin ligand pathway in vivo to reduce the capacity of the **myeloma** cells to survive and proliferate, are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a method (I) for treating multiple **myeloma**, comprising administering an antagonist of the reaction between an alpha4 subunit-bearing integrin and a ligand for an alpha4 subunit-bearing integrin;

(2) a method (II) for inhibiting bone reabsorption associated with bone marrow tumors, comprising administering an antagonist of the reaction between an alpha4 subunit-bearing integrin and a ligand for an alpha4 subunit-bearing integrin; and

(3) a method (III) for treating a disorder characterized by osteoclastogenesis, comprising administering an antagonist of the reaction between an alpha4 subunit-bearing integrin and a ligand for an alpha4 subunit-bearing integrin.

ACTIVITY - Cytostatic; osteopathic.

18 SCID mice were injected with 5TGM1 **myeloma** cells at day 0. 4 mice were treated with phosphate buffered saline (PBS), 4 mice were treated with in a prophylactic protocol with monoclonal antibody (mAb) M/K-2.7 reactive against mouse VCAM-1 in doses of 80 mu g (4 mg/kg) every 3 days starting at day -1 (i.e. days -1, 2, 5, 8 and 11). In a parallel experiment, using the same protocol, 5 mice were treated with 160 mu g mAb M/K-2.7. in addition, 5 mice were treated with 160 mu g mAb M/K-2.7 starting at day 8 (i.e. days 8, 11, 14, 17 and 20) in a therapeutic protocol. Serum was taken from all mice on days 21, 28 and 35, and the animals were X-rayed and sacrificed for histology on day 35. All 3 treatment groups showed a reduction in serum immunoglobulin G2b levels indicative of reduced **myeloma** cell burden. A significant effect was also observed on spleen weights at the low dose prophylactic protocol relative to the control (0.23 plus or minus 0.14 g for control versus 0.08 plus or minus 0.04 for treated). In the prophylactic high dose group, 4 out of 5 animals showed a clear reduction in spleen weight, but the overall value was not significant due to one of the animals having a large spleen weight.

MECHANISM OF ACTION - The antagonists inhibit the binding of alpha4 integrin and alpha4 integrin ligands which reduces the capacity of **myeloma** cells to proliferate and survive.

USE - The methods may be used for treating multiple **myeloma**, inhibiting the release of bone-reabsorbing factors by **myeloma** cells (which result in severe bone loss, the major side effect of **myeloma** in humans) and other disorders associated with osteoclastogenesis.

Dwg.0/6

FS CPI

FA AB; DCN

MC CPI: B04-B04C2; B04-B04C7; B04-B04L; B04-C01; B04-F02; B04-G01; B04-G02; B04-G21; B04-H01; B04-N02; B11-C07A; B11-C08E1; B11-C09; B12-M05; B14-H01; B14-L06; B14-N02; B14-S11C; D05-H07; D05-H08; D05-H11

TECH UPTX: 20000516

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Methods: In (I), (II) and (III), the antagonist is either an alpha4 integrin binding agent or an alpha4 integrin ligand binding agent. In (I), the alpha4 integrin binding agent may be:

(a) an antibody homolog that antagonizes the interaction of both integrin VLA-4 (cell surface adhesion molecule CD29) and alpha4beta7 with their respective alpha4 ligands;

(b) an antibody homolog that antagonizes the interaction of VLA-4 with it's alpha4 ligand; and/or

(c) an antibody homolog that antagonizes the interaction of alpha4beta7 with it's alpha4 ligand.

The alpha4 integrin ligand binding agent is an anti-VCAM-1 antibody homolog. In (II) and (III), the alpha4 integrin binding agent is an anti-VLA4 antibody homolog or anti-alpha4beta7 antibody homolog and the alpha4 integrin binding agent is an anti-VCAM antibody homolog. The antibody homologes may be human antibodies, chimeric antibodies, humanized antibodies (and/or fragments of them). Alternatively, the antagonists are small molecules.

ABEX UPTX: 20000516

ADMINISTRATION - In (I) and (II) the antagonists (antibodies or small molecules) are administered in doses of 0.1 - 30 (especially 0.1 - 20) mg/kg of body weight (claimed). The antagonists may be administered parenterally.

EXAMPLE - 18 SCID mice were injected with 5TGM1 myeloma cells at day 0. 4 mice were treated with phosphate buffered saline (PBS), 4 mice were treated with in a prophylactic protocol with monoclonal antibody (mAb) M/K-2.7 reactive against mouse VCAM-1 in doses of 80 micrograms (4 mg/kg) every 3 days starting at day -1 (i.e. days -1, 2, 5, 8 and 11). In a parallel experiment, using the same protocol, 5 mice were treated with 160 micrograms mAb M/K-2.7. in addition, 5 mice were treated with 160

micrograms mAb M/K-2.7 starting at day 8 (i.e. days 8, 11, 14, 17 and 20) in a therapeutic protocol. Serum was taken from all mice on days 21, 28 and 35, and the animals were X-rayed and sacrificed for histology on day 35. All 3 treatment groups showed a reduction in serum immunoglobulin G2b levels indicative of reduced myeloma cell burden. A significant effect was also observed on spleen weights at the low dose prophylactic protocol relative to the control (0.23 +/- 0.14 g for control versus 0.08 +/- 0.04 for treated). In the prophylactic high dose group, 4 out of 5 animals showed a clear reduction in spleen weight, but the overall value was not significant due to one of the animals having a large spleen weight.

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=> d his

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L1            1 S E3
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L2           79 S E3 AND 46.150.18/RID AND 1/NR
L3           67 S L2 NOT PHENYLALANINE
L4           61 S L3 NOT ALANINE
L5           18 S L2 NOT L4
L6            5 S L5 AND 4
L7            3 S L6 NOT (T/ELS OR 14C2)
L8            3 S L1,L7
                SEL RN
L9           24 S E1-E3/CRN
L10          18 S L9 NOT PMS/CI
L11          17 S L10 NOT C5-C6-C6-C6/ES
L12           6 S L9 NOT L10
L13           1 S L12 AND 1/NC

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L14        2851 S L8
L15        2642 S MELPHALAN OR MELFALAN
L16        1027 S SARCOCLORIN# OR SARCOLYSIN# OR SARKOLYSIN# OR MEDPHALAN OR ME
L17         260 S NSC241286 OR NSC8806 OR NSC()(241286 OR 241 286 OR 8806) OR 3
L18         268 S L11
L19           2 S L13
L20           9 S MERPHALAN OR MERFALAN
L21         399 S 3 P BIS 2 CHLOROETHYL AMINO PHENYL (L) ALANINE
L22         786 S SARCOLYSIN#

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L23           1 S E3
                SEL RN
L24          57 S E1/CRN
L25           2 S L24 NOT MXS/CI

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L26        1481 S L23 OR L25
L27        1755 S THALIDOMID#
L28          83 S TALINOL OR TALIMOL OR SUARAMIDE OR SOFTENON OR SOFTENIL OR SE
L29           0 S NSC527179 OR NSC66847 OR NSC()(527179 OR 527 179 OR 66847 OR

     FILE 'REGISTRY' ENTERED AT 07:46:57 ON 19 DEC 2003
                E ERYTHROPOIETIN/CN
L30           1 S E3
                SEL RN
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L31           6 S E1/CRN
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L32        1239 S E3
L33        1233 S L32 AND 1/NC

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L34        7864 S L30
L35        8120 S L33
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L37        4034 S L14-L22
L38       12363 S L26-L29,L34-L36
L39       29773 S IL6 OR IL15 OR (IL OR INTERLEUKIN)()(6 OR 15)
                E INTERLEUKIN/CT
                E E45+ALL
L40        1360 S E8,E7
                E E6+ALL
L41       19943 S E40,E58
L42        2073 S L39-L41 AND ANTAGON?
                E MULTIPLE MYELOMA/CT
                E E3+ALL
L43        6756 S E7-E10,E6
L44       16144 S E6-E13,E15-E16/BI
L45         258 S KAHLER? DISEASE OR KAHLER S DISEASE OR (PLASMA!CELL OR PLASMA
                E E17+ALL
L46       16171 S L43-L45
                E BISPHOSPHON/CT
                E DIPHOSPHON/CT
                E E6+ALL
                E E2+ALL
L47        2833 S E4
L48        6253 S (DIPHOSPHORIC OR BISPHOSPHORIC)()ACID OR DIPHOSPHONATE OR BIS

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L49           1 S 13598-36-2

     FILE 'HCAPLUS' ENTERED AT 07:56:33 ON 19 DEC 2003
L50        3228 S L49/D
L51       10651 S L47,L48,L50

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L53             STR
L54          50 S L53
L55      103129 S L53 FUL
L56       47349 S L55 AND 2/P
L57       46762 S L56 NOT SQL/FA
L58       46596 S L57 NOT MXS/CI
L59       44634 S L58 NOT PMS/CI
L60       37599 S L59 NOT (COMPD OR WITH OR UNSPECIFIED OR IDS/CI)
L61        9750 S L56 NOT L60

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L64      138425 S L38,L42,L51,L62,L63
L65         601 S L64 AND L46
L66        2928 S (ALPHA4 OR ALPHAIV OR 4ALPHA OR IVALPHA OR ALFA4 OR ALFAIV OR
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                E E11+ALL
L67        2296 S E2
L68        1570 S E4
L69           5 S L65 AND L68
L70           5 S L65 AND L67
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L71          412 S L14-L22 AND L46
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L73            8 S L69,L70,L72
L74            9 S L71 AND INTEGRIN
L75           19 S L65 AND INTEGRIN
L76           25 S L73-L75
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                 E MUNDY G/AU
L77          279 S E3,E6,E8-E10
                 E YONEDA T/AU
L78           67 S E3
                 E YONEDA TOSH/AU
L79          129 S E4,E16-E19
L80            2 S L76 AND L77-L79
L81            7 S L76 AND (PD<=19990913 OR PRD<=19990913 OR AD<=19990913)
L82            7 S L80,L81
L83           46 S L14-L22,L64 AND L67,L68
L84          580 S L14-L22,L64 AND INTEGRIN
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L86           84 S L85 AND (PHARMACOL? OR PHARMACEUT?)/SC,SX
L87           71 S L85 AND IMMUN?/SC,SX
L88          138 S L86,L87
                 E BONE/CT
                 E E3+ALL
L89           18 S L85 AND E9,E8+NT
                 E E33+ALL
L90           23 S L85 AND E7,E8,E6+NT
                 E E118+ALL
L91            7 S L85 AND (E31+NT OR E32+NT OR E34+NT OR E35+NT OR E36+NT OR E3
L92           35 S L89-L91
                 SEL DN AN 1 3 15 20 22 23
L93            6 S L92 AND E1-E18
L94           10 S L82,L93 AND L14-L22,L26-L29,L34-L48,L50,L51,L62-L93
                 SEL HIT RN

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L95           11 S E19-E29

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                 SEL RN L80

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L96           19 S E30-E48
L97           15 S L96 NOT L95

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L98         6258 S L14-L22
L99            3 S L98 AND INTEGRIN
L100           2 S L99 AND PY<=1999

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L101       13444 S L14-L22
L102          15 S L101 AND INTEGRIN
L103           7 S L102 AND PY<=1999
L104           2 S L103 AND MYELOMA

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L105           3 DUP REM L100 L104 (1 DUPLICATE REMOVED)
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                 E E3+ALL
L107         271 S E2 OR 1166/DRN
                 E THALIDOMIDE/DCN
                 E E3+ALL
L108         125 S E2
L109         194 S L27/BIX OR L28/BIX
L110        1260 S L36/BIX
                 E ERYTHROPOIETIN/DCN
L111        1619 S L39/BIX
L112        1215 S L48/BIX
L113        6479 S PYROPHOS?/BIX
L114         347 S PYRO PHOS?/BIX
L115       11129 S L106-L114
L116         125 S L115 AND INTEGRIN/BIX
L117          12 S L116 AND (L44/BIX OR L45/BIX)
L118          13 S L116 AND MYELOM?/BIX
L119          13 S L117,L118
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L120          29 S E3,E5
                 E YONEDA T/AU
L121         240 S E3,E4
L122           7 S L115 AND L120,L121
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L125           1 S L124 AND MYELOM?
L126          14 S L119,L125
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L127           2 S L126 AND E1-E4

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